An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)±

Literature review on serogroup B invasive meningococcal disease: epidemiology, multicomponent meningococcal B vaccine characteristics and other factors for consideration

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of the Agency's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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I. INTRODUCTION

I.1. BACKGROUND

Serogroup B invasive meningococcal disease (IMD) is the most common type of IMD in Canada with an average annual incidence of 0.33 cases per 100 000 population from 2005 to 2010 (National Enhanced Invasive Meningococcal Disease Surveillance System: National Microbiology Laboratory and Centre for Immunization and Respiratory Infectious Diseases [CIRID], Public Health Agency of Canada [the Agency]). While rates are low compared to other infectious and non-infectious disease, infants less than one year of age are at especially high risk and infection is associated with high case fatality (10.7% in Ontario from 2000-2010,(1) 4.6% in Canada from 2005-2010 [CIRID, Agency]) and morbidity, such as sensorineural hearing loss, cognitive deficits and limb loss.

Neisseria meningitidis (meningococci) are classified into at least 13 different serogroups according to the immunologic reactivity of the capsule polysaccharides,(2) of which five serogroups (A, B, C, W-135 and Y) are frequently associated with invasive disease.(3) Additional classification is based on Porin A or class 1 outer membrane proteins (sero-subtype), Porin B or class 2 or 3 outer membrane proteins (serotype), and lipooligosaccharides (immunotype).(2) The polysaccharide capsule provides the basis for the currently licensed meningococcal vaccines of which the following are approved for use in Canada: three monovalent meningococcal conjugate vaccines for serogroup C (Menjugate®, Neis Vac-C® and Meningitec™), two quadrivalent meningococcal conjugate vaccines for serogroups A, C, Y and W-135 (Menactra® and Menveo™) and one quadrivalent polysaccharide meningococcal ACYW-135 vaccine (Menomune®).

Unlike serogroups A, C, W-135 and Y, serogroup B capsular polysaccharide is composed of α2-8–linked polysialic acid which is also found in human neural cell adhesion molecule (nCAM). Because their capsular polysaccharide is similar to human tissue, a polysaccharide vaccine would be poorly immunogenic and could cause autoimmunity in those vaccinated. As such, a capsular vaccine has not been pursued.

Instead, the focus of vaccine development has largely been on outer membrane vesicles (OMVs) and other surface exposed protein antigens. Single component serogroup B OMV vaccines developed in meningococcal serogroup B outbreak settings, and sometimes combined with meningococcal polysaccharide (for example, VA-MENINGOC-BC® in Cuba and Brazil; MenBvac® in Norway; and MeNZB™ vaccine in New Zealand) appear to be safe and effective, however they offer protection only against the outbreak strain for which they were developed.(4) Efforts have been ongoing to develop a more generic serogroup B vaccine by way of identifying surface exposed protein antigens that induce bactericidal activity against a wide range of meningococcal B strains. At the time of this review, two protein based vaccines are in advanced stages of clinical development.

Pfizer's meningococcal serogroup B recombinant lipoprotein (rLP2086) vaccine targets two families of the outer membrane lipoprotein, LP2086 (also known as factor H binding protein), identified using conventional biochemical purification methods. rLP2086 vaccine is currently being tested in humans with recruitment for phase III trials scheduled to begin in late 2012/2013 (clinicaltrials.gov NCT01352793, NCT01352793).

Novartis' multicomponent meningococcal serogroup B (4CMenB) vaccine has recently been submitted for licensure and contains the OMV (PorA) from the New Zealand MeNZB™ vaccine, plus five recombinant proteins identified by reverse vaccinology: factor H binding protein (fHbp), Neisserial adhesion A (NadA) Neisserial heparin binding antigen (NHBA), genome-derived neisserial antigen 2091 (GNA2091), and genome-derived neisserial antigen 1030 (GNA1030).

I.2. PURPOSE/OBJECTIVES

The first serogroup B meningococcal vaccine, 4CMenB, submitted for licensure under the trade name Bexsero™ (Novartis Vaccines), was authorized for use in Canada on December 6, 2013. The purpose of this report is to provide the National Advisory Committee on Immunization (NACI) with a comprehensive summary of 4CMenB vaccine to support the development of evidence-based recommendations on the use of this meningococcal B vaccine in Canada. Specifically, the primary objective was to conduct a systematic search and literature review to identify and synthesize the available body of evidence on 4CMenB vaccine.

This report begins by providing readers with a description of the vaccine and related technology which includes correlates of protection for protein based vaccines, measures of immunogenicity and the meningococcal antigen typing system (MATS). The bulk of this report describes the methods and findings of a systematic review of the efficacy, immunogenicity, effectiveness and safety of 4CMenB vaccine. Also included is a comprehensive (but non-systematic) review of the efficacy, immunogenicity, effectiveness and safety of its precursor vaccine, MeNZB™ (Novartis Vaccines, formerly Chiron), the New Zealand OMV (NZ-OMV) vaccine developed to protect against an epidemic strain of serogroup B meningococcus in that country. Other characteristics of the 4CMenB vaccine, including its administration and proposed schedule, serological testing, storage requirements, simultaneous administration with other vaccines, and contraindications and precautions are discussed briefly. The report concludes with a discussion of the evidence gaps and ongoing surveillance needs as identified by the literature review.

II. TECHNOLOGY

II.1. PREPARATION(S) AUTHORIZED FOR USE IN CANADA

4CMenB vaccine (Bexsero®, Novartis Vaccines), a multicomponent meningococcal serogroup B vaccine, is the first vaccine against serogroup B meningococcus to be approved for use in Canada. The vaccine is a white, opalescent, liquid suspension. Each 0.5 mL pre-filled syringe for intramuscular injection contains 50 µg each of two recombinant fusion proteins of surface-exposed meningococcal proteins, 50 µg of a single recombinant meningococcal surface protein and 25 µg of detoxified porin A (PorA) OMVs, all of which are described in further detail below.

The meningococcal surface proteins contained within the vaccine were identified using a process called reverse vaccinology, a novel vaccine development technique that relies on accepted molecular biology laboratory methods. The proteins selected for inclusion in 4CMenB vaccine were based on their immunogenicity in mice. The genome of *N. meningitidis* serogroup B (strain MC58) was sequenced; 570 DNA sequences likely to encode meningococcal surface proteins were found via whole genome screening; and 350 of these sequences were inserted into an *Escherichia coli* expression system to produce recombinant proteins. These purified proteins were examined in murine immunization studies and ultimately five recombinant protein antigens that both elicited high serum bactericidal antibody (SBA) titres and were conserved among serogroup B meningococcal strains were included in 4CMenB vaccine(5) The five proteins are neisserial adhesion A (NadA), factor H binding protein (fHbp), neisserial heparin-binding antigen (NHBA), genome-derived neisserial antigen 2091 (GNA2091), and genome-derived neisserial antigen 1030 (GNA1030).

Research into the multiple roles each of these proteins may play in the organism-host relationship is ongoing but some of their functions are known and described below. NadA promotes adherence to and invasion into human epithelial cells.(6) There are five variants of NadA with numerous sub-variants. Three variants (1, 2 and 3) are highly cross-reactive,(7) fHbp assists in iron-uptake (which is necessary for bacterial survival).(8) It also binds the complement control protein factor H to thwart an appropriate alternate pathway complement response to meningococcus by the human body.(9) There are three variants of fHbp (1, 2 and 3) and, according to preclinical studies, cross-reactivity is good among sub-variants of variant 1, and more so in adults than in infants, but poor between variants.(10) fHbp is also known as LP2086. NHBA binds heparin and seems to promote meningococcal survival in human serum.(11) NHBA may also adhere to glycosaminoglycans on host tissues. Preclinical data suggest that the majority of NHBA peptides are cross-reactive.(12) The specific functions of GNA2091 and GNA1030 are unknown.

The two recombinant fusion proteins included in 4CMenB vaccine are 50 µg of fHbp, Novartis sub-variant 1.1, joined to GNA 2091 (fHbp-GNA 2091) and 50 µg of NHBA, peptide 2, fused to GNA 1030 (NHBA-GNA 1030). Fusion increased stability (*personal communication with Novartis*) and immunogenicity in studies of the candidate vaccines.(13) The third component of 4CMenB vaccine is 50 µg of recombinant NadA, sub-variant 3.1, as a single recombinant protein, not fused to any others. The recombinant proteins are prepared through molecular technology using plasmid vectors that perform extrachromosomal DNA expression vectors in *E. coli* cells (Product Monograph, May 2011).

The fourth component is 25 µg of detoxified PorA OMVs from *N. meningitidis* NZ98/254 (B:4:P1.7-2,4: ST-42 cc41/44). To produce the OMV antigen, strain NZ98/255 meningococci are grown in a fermentor, after which the bacteria are inactivated with deoxycholate, which also mediates formation of the outer membrane components into vesicles, the OMV (Product Monograph, May 2011). In trials comparing the candidate vaccine with and without the OMV component, in addition to inducing specific antibodies to the reference strain, the OMV appears to have an adjuvant effect on the immunogenicity of the other components of the vaccine.(13)

The three recombinant protein components are adsorbed onto 1.5 mg aluminum hydroxide, an adjuvant. Each 0.5 mL of 4CMenB vaccine contains 10 mmol of histidine in 3.25 mg of sodium chloride, a non-medicinal buffer. 4CMenB vaccine does not contain thimerosol or *E. coli*. If Health Canada's Biologics and Genetic Therapies Directorate (BGTD) approves the vaccine as was submitted, 4CMenB vaccine may be used in persons aged 2 months and older.

II.2. CORRELATES OF PROTECTION

Experiments conducted on military recruits by Goldschneider and co-authors demonstrating a correlation between human serum bactericidal assay (hSBA) titres of ≥4 and protection from serogroup C IMD,(14) led to the accepted use of hSBA as surrogate marker, or correlate, of protection for all meningococcal groups. hSBA quantifies the ability of serial dilutions of human serum to kill a standard small inoculum of *N. meningititis* in the presence of complement.(15) Human complement (including human factor H complement regulatory protein) should ideally be used to perform SBA. Due to lack of availability of human complement, rabbit complement can also be used in the SBA and this is referred to as rSBA. However, rabbit complement factor H does not bind to *N. meningitidis* and leads to overestimation of vaccine efficacy.(16) In human infection, the binding of factor H to the bacterial surface down regulates the human complement activation that otherwise assists in fighting the invading bacteria. Because the complement cascade in rabbit sera is not impaired by neisserial factor H binding proteins, the immune response is more robust, yielding higher SBA titres.(16) All immunogenicity studies of 4CMenB vaccine use hSBA, not rSBA. It should be noted that while hSBA is the accepted correlate of protection for meningococcal disease, there is a body of literature examining other important factors in the immune pathway that contribute to the human immune response to meningococci. This includes opsonophagocytic activity.(17)

For serogroup B IMD, the proportions of vaccines with ≥4-fold rises in hSBA pre- to post-vaccination or hSBA titres of ≥1:4 have been associated with efficacy in OMV vaccine trials.(16) These hSBA titres are in the context of exposure to a meningococcal strain with the same PorA OMV as the vaccine. Limitations of the hSBA assay for meningococcal serogroup B protein vaccines, however, include substantial inter-laboratory variation, a lack of consensus about representative target strains and difficulty in getting human complement sources for all test strains.(16) Despite limitations, hSBA was used to measure the immunogenicity of 4CMenB vaccine against four serogroup B meningococcal strains, as described below.

II.3. MEASUREMENT OF IMMUNOGENICITY

Meningococcal serogroup B strains H44/76 (B:15:P1.7,16: ST-32 cc32), N5/99 (B:2b:P1.5,2: ST-1349 cc8) and NZ98/254 (B:4:P1.7-2,4: ST-42 cc41/44) were used to determine responses against 4CMenB vaccine components fHBP (Novartis sub-variant 1.1), NadA (sub-variant 3.1) and PorA (sero-subtype 1.4), respectively (see Table 1, below). Responses to vaccine antigen NHBA (peptide 2) were assessed using strain

M10713 (B:ND:P1.17,16-3: ST-136 cc41/44) or, prior to the very recent identification of M10713 as a good strain for assessing NHBA immunogenicity, serum immunoglobulin G (IgG) to NHBA was measured after immunization.

Table 1: N. meningitidis serogroup B strains used to measure immunogenicity

	Strain characterization						
Strain	**Serotype/ sero-subtype**	**Sequence type**	**Clonal complex**	**PorA (VR2)**	**fHBP†**	**NadA**	**NHBA**
NZ98/254	B:4:P1.7-2,4	42	41/44	P1.4	1.14	^{x}	1.2
H44/76	B:15:P1.7,16	32	32	P1.16	1.1	^{x}	2.1
N5/99	B:2b:P1.5,2	1349	8	P1.2	2.8	2.2	11.4
M10713	B:ND:P1.17,16-3	136	41/44	P1.16-3	2.9	^{x}	10

†Novartis classification scheme; ^{x} strain does not harbor the NadA gene. Antigen variants or peptides underlined with a solid line are homologous with those contained in 4CMenB vaccine. Antibodies against vaccine antigen NadA sub-variant 3.1 are considered cross-reactive with NadA sub-variant 2.2 found in strain N5/99 (7); similarly, preclinical data suggest that antibodies elicited against vaccine antigen NHBA peptide 2 will be cross-protective against strains expressing different NHBA peptides, including peptide 10 found in strain M10713 (*communication with Novartis on June 13, 2012*).

Each reference strain was selected for use in 4CMenB vaccine trials because three of four major vaccine antigen components were not expressed, expressed in low levels or expressed in a variant mismatched to the variant contained in the vaccine with no cross-reactivity in the SBA.(13) In other words, the hSBA titres to each strain act as a proxy for the immune response stimulated by each protein. For example, strain H44/76 expresses homologous fHbp Novartis sub-variant 1.1, heterologous NHBA and PorA, and does not harbor the NadA gene; thus, an hSBA titre when serum is exposed to strain H44/76 is considered to represent bactericidal activity to fHBP.(18)

Antibodies against vaccine antigen NadA sub-variant 3.1 are considered cross-reactive with NadA sub-variant 2.2 found in strain N5/99.(13) Similarly, preclinical data suggest that antibodies elicited against vaccine antigen NHBA peptide 2 will be cross-protective against strains expressing different NHBA peptides,(12) including peptide 10 (*personal communication with Novartis*).

SBA responses induced by OMV vaccines are largely specific to the sero-subtype (PorA). The PorA of the epidemic strain, NZ98/254, in New Zealand was P1.7-2,4.

II.4. MENINGOCOCCAL ANTIGEN TYPING SYSTEM

4CMenB vaccine targets surface exposed meningococcal proteins, as described above. Different meningococcal strains including non-serogroup B strains, express each of these proteins to different extents. This makes it difficult to predict how well the vaccine will prevent serogroup B disease caused by strains for which immunogenicity has not been tested. Further, it is not practical to test hSBA responses to many hundreds of serogroup B serotypes and sero-subtypes using sera of trial participants. To overcome this challenge, Novartis developed the meningococcal antigen typing system (MATS), as described by Donnelly and colleagues.(19) This is referred to as the MATS assay.

The proprietal MATS assay uses antigen-specific enzyme linked immunosorbent assay (ELISA), which measures the immunologic cross-reactivity and quantity of NHBA, NadA and fHbp antigens in a meningococcal isolate of a given strain. If quantities of the proteins expressed and their relative cross-reactivities with the vaccine components detected are relatively high, it is predicted that the vaccine will be protective against that strain. In addition to the MATS assay, PorA genotyping information from the tested meningococcal strains is also used to predict if 4CMenB vaccine will produce an immune response to them. Rabbit anti-sera against the three proteins were used to create the antibodies needed for ELISA (nb: in this case, rabbit serum is appropriate as, regarding fHBP, an anti-fHBP is made by the rabbit serum. This is independent of the ability of meningococcal fHBP to bind, and inhibit, rabbit factor H).(19) The MATS assay is an antigen-specific sandwich ELISA whereby detergent extracts of standardized amounts of *N. meningitidis* strains were added to different ELISA plates pre-coated individually with rabbit antisera to NHBA, NadA and fHbp. The degree to which a given bacterial strain 'sticks' on an ELISA plate is directly correlated to how much of the targeted protein is expressed by the tested bacterial strain (e.g., NHBA antisera captures NHBA expressed by the test organism). To quantify the amount of target proteins expressed by the test strain, two-fold serial dilutions of the test extract are added to the antibody coated ELISA plate. In separate ELISA wells, standardized amount of extracts prepared from reference strains are also added. The captured target protein is then detected in a sandwich manner by another rabbit antibody to the protein and this secondary antibody is biotinylated for reaction with an enzyme labelled streptavidin which upon reaction with the substrate will provide the colour signal for quantitation. Comparison of the signal given by the test strain to that of the reference strain will provide the 'relative potency' or RP of the test strain.

To determine what RP in the MATS assay will correlate to protection, a set of strains were tested by both MATS and hSBA using pooled sera from vaccine study participants demonstrating significant hSBA titres (either a titer of ≥8 if pre-immunization titres <4 or a four-fold rise in SBA titer if pre-immunization titer ≥4). The lowest RP given by strains that were killed in the hSBA were termed the positive bactericidal threshold (PBT). Higher SBA titres were correlated with higher MATS RP in the study.(19) According to this study, the PBTs for fHBP, NHBA, and NadA were set at 2.1%, 29.4%, and 0.9% RPs.

After the MATS assay is performed, additional information is obtained by simply matching PorA genotype. If a given strain has the same PorA genotype as the NZ strain in 4CMenB vaccine, the vaccine is considered to protect against the strain. Therefore, meningococcal serogroup B strain coverage was defined by the authors as the proportion of strains "that demonstrate a relative potency above the positive bactericidal threshold for at least one vaccine antigen in the MATS ELISA or are matched to the PorA subtype of4CMenB" vaccine.(19) Through validation of the assigned positive bactericidal thresholds, it has been demonstrated that MATS may be a conservative predictor of 4CMenB vaccine protection against a variety of meningococcal strains. For example, using 124 meningococcal strains, 85% were "killed" based on hSBA of pooled adult sera whereas MATS only predicted 72% (95% CI: 55-81%).(19) That said, MATS is an *in vitro* prediction of protection and true protection against serogroup B meningococcal disease in the population remains unknown. The results of MATS research in the UK and Canada are presented in Section IV below.

III. VACCINE EFFICACY, IMMUNOGENICITY, EFFECTIVENESS AND SAFETY

III.1METHODS

A comprehensive literature search strategy was developed with assistance from Library Services at Public Health Ontario, to identify relevant evidence on the candidate meningococcal serogroup B vaccine, 4CMenB vaccine. The search strategy used a combination of subject headings and text words related to the organism AND vaccine AND efficacy/ immunogenicity/ effectiveness/safety outcomes to adequately address the broad set of research questions. In anticipation that there would be no efficacy or effectiveness data available on 4CMenB vaccine, similar search terms for the NZ-OMV vaccine (MeNZB™, Novartis Vaccines, formerly Chiron), a component of 4CMenB vaccine for which there is effectiveness data available, were also included in the search strategy. The search terms varied based on subject headings used by different databases, and are presented in Appendix 1 for Medline.

Six electronic databases were systematically searched on January 4th, 2012 (Medline <1946 to present>; Embase <1974 to 2012 January 3>; PsychINFO <1987 to December Week 4 2011>; CINAHL <1981 to present>; Cochrane Database of Systematic Reviews; and Cochrane Central Register of Controlled Trials) and returned 8136 records. The search was then narrowed to articles in English and humans published from 2005 to present, yielding 2459 records. The date restriction (2005 to present) was selected based on the rationale that trial results using the OMV (PorA) component of the vaccine used in New Zealand were first published in 2005 (20), and recruitment for Novartis phase II trials using the candidate Meningococcal Serogroup B Vaccine began early 2006 (clinicaltrials.gov). After removing 581 duplicates, 1878 records were identified by the search strategy.

Titles and abstracts of all records were independently screened against eligibility criteria by two reviewers in parallel using web-based systematic review software (DistillerSR, Evidence Partners, Ottawa, ON, Canada). The primary inclusion criteria were English-language studies (phase II or III clinical trials) assessing the efficacy, immunogenicity, effectiveness or safety of 4CMenB vaccine in humans. The secondary inclusion criteria were English-language studies assessing the effectiveness of NZ-OMV vaccine (MeNZB™) in humans. A total of 55 records were retained for full text review. As the focus of this review is on 4CMenB vaccine, pre-licensure (phase II and III) clinical trials and post-licensure safety surveillance studies on NZ-OMV vaccine were excluded and incorporated as supporting information. Similarly, papers that provided insights into *a priori* defined points of discussion (e.g., correlates of protection, strain 'coverage') were flagged and incorporated as supporting information. Review papers, letters, opinion pieces, commentaries and studies of other meningococcal serogroup B vaccines, including rLP2086 vaccine (under development; Pfizer), were excluded.

An updated search of the six databases was conducted on February 27th, 2012, using the same language and date restrictions. This yielded 40 new records (and 26 duplicates). Of these, two additional primary research articles evaluating 4CMenB vaccine were identified and included in the review.(21),(22) A new search of these same six databases was performed on January 2nd, 2013. This yielded 393 new records (and 87 duplicates). Titles and abstracts of all 306 records were screened against eligibility criteria by one reviewer. The search did not identify any peer-reviewed papers published since February 27th, 2012 that assesses the efficacy, immunogenicity, effectiveness or safety of 4CMenB vaccine in humans. Subsequently, a paper meeting inclusion criteria was published on January 14th, 2013. Data from this paper had already been included in the literature review (from conference posters) but additional details provided in the paper were added to the present report.

Further, on November 30th, 2012, the titles of abstracts from the 2012 International Pathogenic Neisseria Conference and the 2012 European Society for Paediatric Infectious Diseases meeting were screened by a single reviewer. Six titles (representing three unique trials) met inclusion criteria and these posters were obtained from the manufacturer.

A final search of articles published in Medline since January 2nd, 2013, was conducted on November 7th, 2013, and yielded 112 results. Screening of titles and abstracts was conducted by one reviewer and identified two additional articles from which the data had previously been reported in conference posters.

Eight peer-reviewed papers and nine conference abstracts met the primary inclusion criteria for 4CMenB vaccine. To ensure scientific rigour, data extraction from these 4CMenB vaccine studies was performed by two independent reviewers in parallel using electronic data extraction forms (with the exception of 2012 conference posters and the supplementary literature searches conducted on January 14th and November 7th, 2013, for which data was extracted by a single reviewer). Additional data in the form of 11 conference posters and unpublished data on file with Novartis were provided by the manufacturer; and study information from clinicaltrials.gov was used to supplement published papers and conference posters from those trials not yet published. Across all sources, eight papers and 11 conference posters reporting data from twelve phase II or phase III trials on 4CMenB vaccine were included in this review. An additional four papers on NZ-OMV vaccine effectiveness were included under the secondary inclusion criteria; data extraction from these four studies was performed by only one reviewer (i.e., not systematic).

As per the methods of NACI (23), detailed summary tables were prepared which organize the extracted information, and quality assessment was performed by one reviewer. Specifically, each individual study was ranked according to level of evidence (study design) and overall quality (see Table 2 and Table 3, respectively, for specific criteria) using the methods of the third U.S. Preventative Services Task Force described by Harris and colleagues.(24) The US Task Force offers a set of operational parameters or guidelines for evaluating the quality of individual studies across five different designs: systematic reviews, case-control studies, randomized controlled trials, cohort studies and diagnostic accuracy studies.(24) Each study that met the primary or secondary inclusion criteria of this review was rated as good, fair or poor.(24) The quality was assessed for published manuscripts only, and not for the conference posters as the quality assessment of these trials requires information that is expected to be included in published manuscripts but was not included in conference proceedings.

Table 2. Levels of Evidence Based on Research Design

I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 3. Quality (internal validity) Rating of Evidence

Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design specific criteria are outlined in *Harris et al* (2001).(24)

III.2 RESULTS

At the time this review was conducted, eight papers and 11 conference posters reporting data from twelve phase II or phase III trials on 4CMenB vaccine met the primary inclusion criteria of this review. Four NZ-OMV vaccine effectiveness studies met the secondary inclusion criteria. Additional supporting data from four NZ-OMV post-licensure safety surveillance studies are summarized below, and the findings of five phase II or phase III studies assessing the immunogenicity and safety of NZ-OMV vaccine are appended.

III.2.1. EFFICACY AND EFFECTIVENESS OF 4CMENB VACCINE

There are currently no published studies on the efficacy of 4CMenB vaccine and its effectiveness also remains unknown.

III.2.2. IMMUNOGENICITY OF 4CMENB VACCINE

Immunogenicity of 4CMenB vaccine was measured and reported in approximately 5800 participants across twelve trials. These studies are summarized below, and in Table 4, by age group: ≤12 months, 12 to 24 months, 2 to 10 years, 11 to 17 years, and ≥18 years of age.

Infants ≤12 months old

Immunogenicity of 4CMenB vaccine among infants was measured in approximately 3700 healthy participants enrolled in nine clinical trials conducted in Europe and South America.(13),(25),(26),(27),(22),(28),(29),(30),(31),(32),(33) The following infant vaccination schedules were assessed, often with concomitant administration of age-appropriate vaccines: three doses given at 2, 3 and 4 months of age; three doses given at 2, 4 and 6 months of age with or without a booster dose given at 12 months of age; and three doses given at 6 to 8 months of age, 60 days later and 12 months of age.(26),(34)

Two small phase II randomized trials(13),(25) compared the immunogenicity of 4CMenB vaccine to that of a candidate recombinant meningococcal B (rMenB) vaccine, which is 4CMenB vaccine without the OMV component, among infants in UK. Results presented below are only for the complete 4CMenB vaccine, not the rMenB product. In a multicenter trial by *Findlow et al* (2010)(13), 46 of 147 enrolled infants were randomized to receive four doses of 4CMenB vaccine given at 2, 4, 6 and 12 months of age with UK infant vaccines (see Table 4 for co-administered vaccines at each visit). One month after the second and third doses 4CMenB vaccine, 74–100% and 85–95% of infants had an hSBA titre of ≥1:4 against reference strains H44/76, N5/99 and NZ98/254, compared with 9–14% of infants at pre-vaccination baseline. Six months after the third dose of 4CMenB vaccine, before the fourth dose was given, between 34% and 89% of infants met the antibody threshold. One month after the fourth dose, 93–100% of participants had an hSBA titre of ≥1:4 against the reference strains. Responses were lower against UK strains M01 240101 (B:NT:P1.19-1,15-11: ST-1049 cc269), M01 240364 (B:2a:P1.5,2: ST-11 cc11) and M01 240355 (B:1:P1.22,14: ST-213 cc213) which expressed diverse variants of the vaccine antigens, with antibody levels achieved by 0–47% one month after dose three and 4–75% one month after dose four. Seroconversion, defined as a 4-fold or greater rise in hSBA titre compared with pre-vaccination baseline (≥8 for those with hSBA titre <2 before vaccination), was achieved against strains H44/76, N5/99 and NZ98/254 by 55–94% of infants one month after dose two; 78–92% of infants one month after dose three; and 84–97% of infants one month after dose four. Overall, antibody geometric mean titres (GMTs) were lower for reference strain NZ98/254. GMTs for strains H44/76, N5/99 and NZ98/254 were as follows: 28.0, 104.0 and 6.6 one month after dose two; 30.0, 126.0 and 19.0 one month after dose three; and 106.0, 629.0 and 29.0 one month after dose four. In summary, 4CMenB vaccine stimulated hSBA titres of ≥1:4 in 74–100% of infants after at least two doses. However, at six months following the third dose, between 11% and 66% of infants no longer met the antibody threshold (prior to receiving dose four).

In a single-center trial by *Snape et al* (2010)(25), 30 of 60 enrolled infants were randomized to receive 4CMenB vaccine given at 6-8 months of age, 60 days later and 12 months of age. Meningococcal serogroup C and Hib vaccine (MCCV-Hib; Menitorix®, GlaxoSmithKline) was also administered at 12 months of age. One month after two or three doses of 4CMenB vaccine, 95–100% of infants had an hSBA titre of ≥1:4 against all three reference strains (H44/76, N5/99 and NZ98/254), compared with 0–29% at pre-vaccination baseline. GMTs for each of the three reference strains one month after vaccination were between 27 and 534 after the second dose and between 44 and 906 after the third dose, compared to between 1 and 1.70 at baseline. NHBA-GNA1030 specific IgG geometric mean concentrations (GMCs) were 2912 µg/mL (95% confidence interval [CI]: 2178, 3894) after dose two versus 3521 µg/mL (95% CI: 2739, 4527) after dose three, compared to 21 µg/mL (95% CI: 18, 24) at baseline. In summary, hSBA titres of ≥1:4 against the three reference strains were reached in ≥95% of infants after at least two doses of 4CMenB vaccine (given at 6-8 months of age, 60 days later and 12 months of age). GMTs were between 27 and 906 against strains H44/76, N5/99 and NZ98/254 (compared to between 1 and 1.70 at baseline) and NHBA IgG GMCs were at least 2912 µg/mL, one month after vaccination.

The immunogenicity of 4CMenB vaccine with and without the use of paracetamol (acetaminophen) among 367 infants in Europe, Argentina and Chile, was compared in a multicenter phase II randomized trial by *Prymula et al* (2011)(26). All 367 infants received three doses of 4CMenB vaccine at 2, 3 and 4 months of age. Half of these infants were randomized to also receive three doses of paracetamol (10-15 mg/kg per dose) accompanying each vaccination (one dose before vaccination, and two further doses separated by 4-6 hours after vaccination). Infanrix-hexa® (GlaxoSmithKline) and Prevenar® (Wyeth Pharmaceuticals, now Pfizer) were also given to all participants. In this study, hSBA titres of ≥1:5 against strains H44/76, N5/99 and NZ98/254 were reached by 100%, 99% and 75–78% of infants, respectively, one month after receiving three doses of 4CMenB vaccine with or without paracetamol.

Vesikari et al (2013)(35) compared three different vaccine lots in a large, multicenter phase III randomized trial conducted in five European countries. Immunogenicity data from this study were initially obtained from a conference poster *Vesikari et al* (2010) (27) as well as from data on file with Novartis, but have since been updated based on the publication. Of 3630 enrolled infants, 1968 were given one of three lots of 4CMenB vaccine at 2, 4 and 6 months of age, along with Infanrix-hexa® (GlaxoSmithKline) and 7-valent pneumococcal conjugate vaccine (Prevenar®, Pfizer). Of these, 1183 were included in the modified intention-to-treat primary immunogenicity analysis against three serogroup B meningococcal reference strains (H44/76-SL, 5/99, and NZ 98/254). The M10713 strain was identified as an appropriate reference strain for NHBA after the study was initiated and, as such, M10713 immunogenicity was only measured in 100 infants. The three lots of 4CMenB vaccine were found to have similar GMTs against each reference strain one month after the third dose of 4CMenB vaccine (GMTs were highest against strain N5/99, ranging from 598 to 681 among the three lots) and were combined by the study authors for the seroprotection analysis. Prior to vaccination, 1–4% of infants had an hSBA titre of ≥1:5 against strains H44/76, N5/99 and NZ98/254, whereas 33% of those assessed had this titre against strain M10713. One month after the third dose, hSBA titres of ≥1:5 were reached by 100% of infants against strains H44/76 and N5/99, and 84% against strains NZ98/254 and M10713.

Gossger et al (2012)(22) compared the immunogenicity of three different 4CMenB vaccination schedules in 1571 out of 1885 infants enrolled in a large multicenter phase IIB trial conducted at 60 sites in six European countries. The three vaccination schedules were as follows: concomitant administration of 4CMenB vaccine with Infanrix-hexa® (GlaxoSmithKline) and 7-valent pneumococcal conjugate vaccines (Prevenar®, Pfizer) given at 2, 4, 6 months of age; concomitant administration of 4CMenB vaccine with Infanrix-hexa® and 7-valent pneumococcal conjugate vaccines given at 2, 3, 4 months of age; or administration of 4CMenB vaccine at 2, 4, 6 months of age alternating with Infanrix-hexa® and Prevenar® given at 3, 5, 7 months of age. A control group of 314 infants received only Infanrix-hexa® and Prevenar® at 2, 3, 4 months of age. A modified intention-to-treat (ITT) population was used in the analysis and included only those who received a study vaccine and provided evaluable serum samples before and after immunization (n=1636, of which 1374 received 4CMenB vaccine and 262 received routine only).

In this study, seroprotection was defined as an interpolated hSBA titre of ≥1:5 against reference strains H44/76, N5/99 and NZ98/254 (this criterion was chosen to ensure the lower level of the 95% confidence interval was above 1:4 for the point estimate). For a statistically significant proportion of children to reach the antibody threshold, the lower level of the 95% confidence interval of the proportion with an interpolated titre ≥1:5 needed to be greater than or equal to 70%, for each of the three reference strains. According to this criterion, seroprotection was achieved in all groups regardless of the infant vaccination schedule one month after the third dose of 4CMenB vaccine with proportions ranging from 79.0% (95% CI: 75.2%, 82.4%) to 100% (95% CI: 98.6%, 100%), compared to between 4.4% (95% CI: 2.2%, 7.7%) and 5.3% (95% CI: 2.8%, 9.1%) in the control group. For reference strains H44/76 and N5/99, the proportion was ≥99% after the third dose of 4CMenB vaccine. For strain NZ98/254, the proportion with hSBA titres of ≥1:5 was greater among infants who received 4CMenB vaccine on a separate occasion from Infanrix-hexa® and Prevenar® (86.1% [95%CI: 82.9%, 89.0%]) compared to all three given together (79.0% [95% CI: 75.2%, 82.4%] for the 2, 4, 6 month schedule; and 81.7% [95% CI: 76.6%, 86.2%] for the 2, 3, 4 month schedule). Similarly, GMTs were consistently lower one month after the third dose of 4CMenB vaccine among infants in the two concomitant groups versus the group that received

4CMenB vaccine on separate occasions from routine vaccines: 82 for the concomitant 2, 4, 6 month schedule and 83 for the concomitant 2, 3, 4 month schedule vs. 110 for the non-concomitant 2, 4, 6 month schedule for strain H44/76; 323 and 520 vs. 669 respectively for strain N5/99; and 11 and 12 vs. 17 respectively for strain NZ98/254. Further, IgG GMCs against NHBA, using a per-protocol population and analyzed as per immunization course received, were also higher when 4CMenB vaccine was given alone (4342 U/ml [95% CI: 4067, 4635]) compared to concomitantly (3332 U/ml [95% CI: 3120, 3558] for the 2, 4, 6 month schedule; and 3211 U/ml [95% CI: 2949, 3495] for the 2, 3, 4 month schedule).

As a secondary immunogenicity endpoint, *Gossger et al* (2012)[22] assessed non-inferiority of the concomitant 2, 4, 6 schedule by comparing the titres achieved one month after the third dose of 4CMenB vaccine, to the titres achieved one month after the third dose of 4CMenB vaccine according to each of the other two schedules (4CMenB vaccine with concomitant routine vaccines at 2, 3, 4 months of age; and 4CMenB vaccine at 2, 4, 6 months of age and routine vaccines at 3, 5, 7 months of age). The pre-specified non-inferiority criterion was defined as 0% difference in the proportion of infants with an hSBA titre, against the reference strain, of ≥1:5 with the lower level of the 95% confidence interval greater than -10%. By this criterion, non-inferiority was met in all comparisons except for the difference in the concomitant 2, 4, 6 month schedule minus the schedule with 4CMenB vaccine given on a separate occasion from routine vaccines, for strain NZ98/254 (-7.1% [95% CI: -11.7%, -2.6%]). The non-inferiority criterion for GMT ratios (defined as a lower level of the 95% confidence interval greater than 0.5 for each reference strain) was met in all comparisons. For example, the GMT ratios of hBSA titres for the concomitant 2, 4 and 6 month schedule divided by concomitant 2, 3 and 4 month schedule, were 1.01 (95% CI: 0.90, 1.49) and 1.10 (95% CI: 0.91, 1.32) for strains H44/76 and NZ98/254, respectively, and slightly higher at 1.61 (95% CI: 1.41, 1.84) for strain N5/99, one month after the third dose of 4CMenB vaccine. In summary, at least 79% of infants had hSBA titres of ≥1:5 after three doses of 4CMenB vaccine. Further, non-inferiority with concomitant vaccines was demonstrated in all comparisons except for one -4CMenB vaccine and routine vaccines given on separate occasions versus given concomitantly at 2, 4, 6 months against strain NZ98/254 (the former group having the higher GMTs).

As an extension of their multicenter lot-comparison trial, described above, *Vesikari et al* (2013)(35) assessed the immunogenicity of a fourth dose of 4CMenB vaccine at 12 months. Data from this study were initially extracted from a conference poster [*Vesikari et al* (2011)(28)] and have since been updated to reflect the publication. In this study, 1555 children previously vaccinated with three doses of 4CMenB vaccine in infancy (according to a 2, 4, 6 month primary immunization schedule) were randomized to receive a fourth dose at 12 months of age with MMRV (Priorix-Tetra™, GlaxoSmithKline), or given separately at 13 months of age. Blood was drawn for immunogenicity measurement in a subset of 437 participants (just over a fourth of those enrolled; *concomitant* group, n=224; *separate* group, n=213). Further, sera from 100 children in the concomitant group were tested against strain M10713. The proportion of children with pre-booster hSBA titres ≥1:5 at 12 months of age were: 81% (355/437) against strain H44/76; 99% (429/434) against strain N5/99; 22% (96/437) against strain NZ98/254; and 61% (61/100) against strain M10713. One month after the booster dose of 4CMenB vaccine (with or without Priorix-Tetra™), all participants (100%) achieved an hSBA titre of ≥1:5 against strains H44/76 and N5/99, whereas 95% met seroprotection criteria for strain NZ98/254 and 97.5% for strain M10713. GMTs and GMT ratios (post- to pre-vaccination) against each of the four reference strains were also similar one month after the booster dose of 4CMenB vaccine given with or without Priorix-Tetra™. In summary, hSBA titres of ≥1:5 against four reference strains were reached in 94–100% of infants after a fourth dose of 4CMenB vaccine given at 12 months, with or without concomitant Priorix-Tetra™.

Immune persistence following 4CMenB vaccine has been assessed at 24 months of life, 12 months after completion of an infant series and 1-year-old booster, as well as at 40 months of life, 28 months after completion of an infant series and 1-year-old booster. In a multicenter phase II/III study by *Kimura et al* (2011)(29), an extension of the *Vesikari et al* (2011)(28) study described above, conducted in Czech Republic and Finland, persistence of the immune response 12 months after a booster dose of 4CMenB vaccine was assessed among 300 children previously vaccinated with 4CMenB vaccine in infancy (given at 2, 4, 6 and 12 months of age). One month after the booster dose, 94–100% of children in this cohort had an hSBA titre of ≥1:5 against strains H44/76, N5/99 and NZ98/254. At 24 months of age, the proportion of children that no longer met the antibody threshold was 38% against strain H44/76, 3% against strain N5/99 and 83% against strain NZ98/254.

In extension to *Findlow et al* (2010)(13), *Saroey et al* (2012)(30), and *Snape et al* (2013)(31) report on immune persistence 28 months after receiving either four doses of 4CMenB vaccine (2, 4, 6, 12 months of life) or a single dose at 12 months of age. Among 19 children who had had the four dose infant series, 65%, 76%, 41%, and 67% had hSBA titres of ≥1:4 against meningococcal strains H44/76, N5/99, NZ98/254, and M10713, respectively. These children were given a fifth dose of 4CMenB vaccine at 40 months of age and immunogenicity was measured one month later. At that time, 95–100% of children met the seroprotection threshold, depending on reference strain. (Results for the group immunized at 12 months of life only are shown in the *Children 12 to 24 months of age* section below.)

Phillip et al (2012)(32) and *Snape et al* (2012)(33) presented the results of a similar extension study of *Snape et al* (2010)(25). In this study, 14 children who had received 4CMenB vaccine at 6, 8, and 12 months of life had seroprotection measured at 40 months of life, prior to receipt of a booster. Prior to the fourth dose of 4CMenB vaccine, hSBA titres ≥1:4 were observed in 35% against strain 44/76-SL, 100% against N5/99, 14% against NZ 98/254, and 79% against M10713. Seroprotection improved after the 4CMenB booster such that one month afterwards, 92–100% of participants met antibody thresholds against the reference strains.

Children 12 to 24 months of age

Immunogenicity of 4CMenB vaccine initiated in children aged 12 to 24 months was measured in approximately 340 healthy participants in four clinical trials in Europe (13),(34),(29),(30),(36). The following vaccination schedules were assessed: a single dose at 12 months of age; two doses at 12 and 14 months of age or 13 and 15 months of age; and a third dose at 24 months of age.

In the *Findlow et al* (2010)(13) study, 23 of 147 enrolled two-month old children were randomized to receive a single dose of 4CMenB vaccine given at 12 months of age, along with UK infant vaccines (note: only Menitorix® was given concomitantly with 4CMenB vaccine at 12 months of age), and immunogenicity was assessed one month later. At 13 months of age, 73% of children had an hSBA titre of ≥1:4 against strain H44/76 and N5/99, compared to 0–18% at pre-vaccination baseline; and 18% had an hSBA titre of ≥1:4 against strain NZ98/254, compared to 0% at pre-vaccination baseline. Seroconversion, defined as a 4-fold or greater rise in hSBA titre compared with pre-vaccination baseline (or ≥ 8-fold for those with an hSBA titre of < 2 before vaccination), was achieved by 36% of children against strain H44/76, 59% against strain N5/99 and 9% against strain NZ98/254. One month post-vaccination, hSBA GMTs were 6.0 (95% CI: 3.5, 10.0), 8.0 (95% CI: 4.2, 15.0) and 1.7 (95% CI: 1.1, 2.5) for strains 44/76, 5/99 and NZ98/254, respectively. In summary, hSBA titres of ≥1:4 against the three reference strains were reached by 18% (against NZ98/254) and 73% (against H44/76 and N5/99) of children one month after a single dose of 4CMenB vaccine (given at 12 months of age with concomitant Menitorix®). Seroconversion was achieved by 9% (against NZ98/254), 36% (against H44/76) and 59% (against N5/99) of children one month after vaccination.

In a multicenter phase II trial by *Prymula, Vesikari, Esposito et al* (2011)(34), conducted in Europe, Argentina and Chile, 402 children who received only routine vaccines, Infanrix-hexa® and Prevenar®, in the *Vesikari et al* (2010)(27) trial described above, were randomized to receive two doses of 4CMenB vaccine given at either 12 and 14 months of age or 13 and 15 months of age. Both groups also received MMRV (Priorix-Tetra™, GlaxoSmithKline) at 12 months of age. Blood was drawn for immunogenicity measurement in a subset of up to 232 participants. Regardless of vaccination schedule, all children (100%) achieved an hSBA titre of ≥1:5 against strains H44/76 and N5/99 one month after the second dose of 4CMenB vaccine, compared to 1.5–5.5% at pre-vaccination baseline (12 months of age). For strain NZ98/254, 96% and 100% of children reached this titre in the 12 and 14 month schedule and 13 and 15 months schedule groups, respectively. GMTs and GMT ratios (post- to pre-vaccination) one month after the second dose of 4CMenB vaccine were similar in both groups, and lowest against strain NZ98/254 with GMTs of 43 (95% CI: 38, 49) in the 12 and 14 month schedule group (with Priorix-Tetra™ also given at 12 months of age) and 32 (95% CI: 26, 40) in the 13 and 15 month schedule group. IgG GMCs (units not provided) for NHBA in each group were 5698 (95% CI: 5030, 6454) and 7154 (95% CI: 5880, 8704) one month after the second dose of 4CMenB vaccine. In summary, 4CMenB vaccine stimulated hSBA titres of ≥1:5 in at least 96% of these 12 to 15 month old children after two doses of 4CMenB vaccine (with or without Priorix-Tetra™ given at the same time).

For children in whom 4CMenB vaccine was initiated between the ages of 12 and 24 months, persistence of seroprotection has been measured 9 to 10 months after last vaccination in one study and 28 months after last vaccination in another small group. In the phase II/III study by *Kimura et al* (2011)(29), an extension of the *Prymula, Vesikari, Esposito et al* (2011)(34) trial described above, persistence of the immune response at 24 months of age was measured in 86 children who previously received 2 doses of 4CMenB vaccine given at either 12 and 14 months or 13 and 15 months of age. In this subset of 86 children, ≥99% had an antibody titre of ≥1:5 against strains H44/76, N5/99 and NZ98/254 one month after the second dose of 4CMenB vaccine (as previously measured in *Prymula, Vesikari, Esposito et al* [2011](34)). At 24 months of age, the following proportions of children no longer met the antibody threshold: 29% against strain H44/76, 3.5% against strain N5/99 and 85% against strain NZ98/254. In a control group of 4CMenB vaccine-naïve children (n=112) aged 24-26 months, ≤3% achieved antibody titres ≥1:5 against the reference strains. The cohort of 86 children received a third dose of 4CMenB vaccine at 24 months of age; one month later, 100% had an against three reference strains were reached in at least 99% of children after two doses of 4CMenB vaccine, given at either 12 and 14 or 13 and 15 months of age. However, 9 to 10 months later, this antibody threshold was no longer reached by 29% (against H44/76), 3.5% (against N5/99) and 85% (against NZ98/254) of infants. A third dose of 4CMenB vaccine given at 24 months of age stimulated hSBA titres of ≥1:5 in 100% of children.

Saroey et al (2012)(30) and *Snape et al* (2013)(31) measured seroprotection at 40 months of age, in 8 children who had received a single dose of 4CMenB at 12 months of age as part of *Findlow* et al (2010)(13) study. Thirty-eight percent had hSBA titre of

≥1:4 against H44/76; 0% against N5/99 and NZ 98/254; and 25% against M10713. In this small group titres improved after booster doses at 40 and 42 months of age such that one month after the second booster, 100% demonstrated seroprotective titres against the four strains.

Children 2 to 10 years of age

The immunogenicity of 4CMenB vaccine initiated in children aged 2 to 10 years has been studied in fewer than 100 children, by two research groups. The "control" group in *Saroey et al* (2012)(30) and *Snape et al* (2013)(31) extension of *Findlow et al* (2010)(13) consisted of 43 4CMenB vaccine naïve children who had immunogenicity measured prior to and one month after each of two doses of 4CMenB vaccine at 40 and 42 months of life. After the first dose, 65-90% had hSBA titres of ≥1:4 against the reference strains. One month after the second dose 100% had hSBA titres of ≥1:4 against strains 44/76-SL and 5/99, 94% had seroprotection against NZ 98/254 and 89% had seroprotection against M10713.

Similarly, *Phillip et al (2012)*(32) *and Snape et al* (2012)(33) gave 4CMenB vaccine to the "control" group in their extension of *Snape et al* (2010)(25). Forty-one toddlers were given two doses of 4CMenB vaccine at 40 and 42 months of life and immunogenicity was measured prior to immunization, as well as one month after each dose. One month after the first dose, 62% had hSBA titres of ≥1:4 against reference strains NZ 98/254 and M10713, 85% had hSBA titres of ≥1:4 to strain 5/99 and 71% had hSBA titres of ≥1:4 to 44/76-SL. Following the second dose, seroprotection improved such that 100% had hSBA titres ≥1:4 to strains 44/76-SL, 5/99, and NZ98/254. 71% had seroprotection against M10713.

Adolescents 11 to 17 years of age

The immunogenicity of one-, two- or three-dose schedules of 4CMenB vaccine was compared in a large multicenter phase IIB/III "placebo controlled" trial by *Santolaya et al* (2012)(21), conducted in six Chilean sites. In total, 1631 adolescents aged 11 to 17 years received four injections given at months 0, 1, 2 and 6; participants were randomized to receive up to three doses of 4CMenB vaccine with a control injection given when a 4CMenB vaccine dose was not scheduled, so that every participant received four injections within 6 months. The 0.5 mL control injection consisted of 1.5 mg of aluminum hydroxide in a 10 mM histidine buffer containing 110-120 mM of saline. 1378 (84%), of 1631 adolescents enrolled, completed assessments after the first three injections given at 0, 1 and 2 months. At 6 months, 1431 (88%) continued their participation, of whom 456 received a dose of 4CMenB vaccine and 975 received a control injection. Serum was collected at baseline and 1 month after each injection. 367 (80%) of 456 who received a dose of 4CMenB vaccine at 6 months and 794 (81%) of 975 who received a control injection at 6 months had sera analysed at 7 months. The primary immunogenicity endpoint was the percentage of participants with a protective hSBA titre of ≥1:4.

One month after receiving the first dose of 4CMenB vaccine, an hSBA titre of ≥1:4 was achieved by more than 90% of adolescents against all tested strains. One month after completing a two or three 4CMenB dose schedule: ≥99% of participants had a titre of ≥1:4 against strains H44/76, N5/99 and NZ98/254, while 92–96% of participants met this criterion one month after completing a one dose schedule. The proportion with hSBA titres of ≥1:4 at pre-vaccination baseline for all adolescents in this study was between 28% and 47%. Among the three-dose vaccination schedules, GMTs (computed controlling for vaccine group and study center) to each reference strain were consistently higher one month after the third dose compared to one month after the second dose, although the 95% confidence intervals overlapped. GMTs were also higher when the second and third doses were administered further apart. For example, one month after the third dose, GMTs against strain H44/76 were 240 (95% CI: 205, 280) when 4CMenB vaccine was given at a 0, 1, 2 month schedule; 259 (95% CI: 188, 357) when given at a 0, 2, 6 month schedule; and 324 (95% CI: 236, 443) when given at a 0, 1, 6 month schedule. The longest duration of follow-up in this study was 7 months after completing a 4CMenB one-dose schedule (4CMenB vaccine given at 0 months); 67% (95% CI: 60%, 74%) to 71% (95% CI: 64%, 78%) of adolescents had an hSBA titre of ≥1:4 against each of the three strains. Six months after completing a 4CMenB two-dose vaccination schedule (4CMenB vaccine given at 0, 1 months), 85% (95% CI: 79%, 90%) to 98% (95% CI: 95%, 99%) met the antibody threshold against each strain. Finally, 94–99% of adolescents met the antibody threshold 5 months after completing either a two-dose schedule (4CMenB vaccine given at a 0, 2 month schedule) or a three-dose schedule (4CMenB vaccine given at a 0, 1, 2 month schedule) of 4CMenB vaccine. In summary, the seroprotection endpoint used in this study was met in all groups except one-at one month after dose 1 (in the group given a 0, 2, 6 month 4CMenB vaccine schedule) against strain H44/76. hSBA GMTs ranged from 187-230 against strain H44/76, 451-880 against N5/99 and 89-140 against NZ98/254 one month after dose 2 of a two-dose schedule of 4CMenB vaccine; and ranged from 240-324 against H44/76, 584-1094 against N5/99 and 122-181 against NZ98/254 one month after dose 3 of a three-dose schedule of 4CMenB vaccine.

In a follow-up study, *Santolaya et al* (2013)(37) measured antibody persistence 18-24 months after receipt of the last dose in 666 participants who received one-, two- or three-doses of the 4CMenB vaccine. For the three test strains, the proportion with hSBA titres of ≥1:4 was lowest among adolescents who received only one dose of the vaccine (62% [95% CI: 53%,70%] to 73% [95% CI: 65%,80%] compared to those receiving two (77% [95% CI: 71%,82%] to 94% [95% CI: 91%,97%]) or three (86% [95% CI: 81%,90%] to 97% [95% CI: 95%,99%]) doses. Study authors also assessed the persistence of seroprotection based on immunization status prior to any vaccination. Among adolescents who lacked bactericidal antibodies at initial study enrolment, 18-24 months after their last vaccination 45% to 57% retained bactericidal titres against strain H44/76, 70% to 93% against strain N5/99, and 77% to 96% against strain NZ98/254. These proportions were generally higher in study participants who displayed seroprotective titres before vaccination, ranging from 90% to 100% against strain H44/76, 97% to 99% against strain N5/99 and 98% to 100% against NZ98/254. In general, higher seroprotection rates and hSBA GMT levels were reported in individuals who received more than one dose of 4CMenB vaccine; hSBA GMT levels for all tested strains were statistically significantly higher following the receipt of two- or three-doses compared to only one-dose.

Adults 18 to 55 years of age

Two studies, including fewer than 100 people, have assessed the immunogenicity of 4CMenB vaccine in healthy adults at risk of occupational exposure to *N. meningitides.* (38),(39) In a multicenter phase II study by *Kimura, Toneatto, Kleinschmidt et al* (2011)(38), conducted at one site in Germany and one site in Italy, 54 healthy laboratory workers aged 18 to 50 years (mean age 31.8 ± 6.1 SD) who were routinely exposed to *N. meningitidis*, were enrolled and given three doses of 4CMenB vaccine using a 0, 2, 6 month schedule. At 7 months, 41 participants also received MenACWY-CRM (Menveo®, Novartis). Study exclusion criteria included previous exposure to someone with laboratory-confirmed *N. meningitidis* infection within 60 days of study enrollment. The per-protocol population included between 25 and 46 participants who provided evaluable sera between 26 and 37 days after an individual vaccine dose. One month after the second dose, 91–100% of participants had an hSBA titre of ≥1:4 to strains H44/76, N5/99 and NZ98/254, compared to 80–88% one month after the first dose and 22–37% at pre-vaccination baseline. Before the third dose was given, 96% (95% CI: 79%, 100%), 100% (95% CI: 86%, 100%) and 67% (95% CI: 45%, 84%) of participants had antibody levels against strains H44/76, N5/99 and NZ98/254, respectively. This proportion reached 92–100% one month after the third dose. Seroconversion, defined as a 4-fold or greater rise in hSBA titre compared with pre-vaccination baseline, was achieved by 64–80% of participants after one dose; 78–100% after two doses; 46–75% before the third dose; and 69–100% after three doses. GMTs one month after dose two, before dose three and one month after dose three were as follows: 93 (95% CI: 71, 121), 26 (95% CI: 15, 47) and 95 (95% CI: 68, 131), respectively, against strain H44/76; 144 (95% CI: 108, 193), 37 (95% CI: 26, 53) and 269 (95% CI: 205, 354), respectively, against strain N5/99; and 32 (95% CI: 21, 48), 9.4 (95% CI: 4.1, 21) and 30 (95% CI: 18, 50), respectively, against strain NZ98/254. In summary, hSBA titres of ≥1:4 were achieved in 80–100% of adults (n=up to 46) after at least one dose of 4CMenB vaccine (given according to a 0, 2, 6 month schedule).

Findlow et al (2012)(39) performed a similar Phase II, single arm study that enrolled 38 public health laboratory workers in the United Kingdom. Participants ranged in age from 23 to 55 years. Participants were given three doses of 4CMenB vaccine, the first simultaneously with MenACWY-CRM (Menveo®, Novartis). 4CMenB vaccine doses were given at 0 months, 3 months and 6 months. Immunogenicity was measured at baseline, prior to the second dose (three months after the first dose), prior to the third dose (three months after the second dose) and one month after the third dose. At baseline, 87% of participants had hSBA titres ≥1:4 against 44/76-SL and 71% had hSBA titres ≥1:4 against NZ 98/254 and 5/99. After three doses, all remaining participants (n=30) demonstrated seroprotection against these three strains. The authors also assessed seroprotection against other meningococcal strains, which will be discussed later in this report.

There are currently no phase II or phase III studies of antibody persistence in adults. The longest duration of follow-up is one month after the third dose, as described above.

Adults >55 years of age

There are currently no studies of the immunogenicity of 4CMenB vaccine in adults over the age of 55 years.

III.2.3. SAFETY OF 4CMENB VACCINE

Safety of 4CMenB vaccine was measured and reported in approximately 8200 participants across eleven of the twelve trials included in this review. These findings are summarized below, and in Table 5, according to the following age groups: ≤12 months, 12 to 24 months, 2 to 10 years, 11 to 17 years, 18 to 55 years, and >55 years of age. Unless noted otherwise, the proportion of reactions or events described below reflect all doses of 4CMenB vaccine combined and were calculated by the review authors.

Infants ≤12 months old

The safety of 4CMenB vaccine among infants was measured in six clinical trials in approximately 4800 healthy participants in Europe and South America.(13),(25),(26),(22),(35),(40),(28)

The *Findlow et al* (2010) and *Snape et al* (2010) trials, conducted in UK, compared the safety of 4CMenB vaccine to that of a recombinant meningococcal B (rMenB) vaccine, which is 4CMenB vaccine without the OMV component. Results presented below are only for the complete 4CMenB vaccine, not the rMenB product. In the *Findlow et al* (2010)(13) open label study, 46 infants were randomized to receive 4CMenB vaccine at 2, 4, 6 and 12 months of age. UK infant vaccines were also administered as follows:

DPTPHib (Pediacel®, Sanofi Pasteur) at 2, 3, 4 months of age; pneumococcal conjugate vaccine (Prevenar®, Wyeth Pharmaceuticals) at 2, 4, 13 months of age; serogroup C meningococcal conjugate vaccine (Menjugate®, Novartis) at 3, 5 months of age; MenC-Hib conjugate vaccine (Menitorix®, GlaxoSmithKline) at 12 months of age; and MMR (Priorix®, GlaxoSmithKline) at 13 months of age. Solicited local and systemic reactogenicity, axillary temperature, any medication administered, any medical attention, and other adverse events were recorded daily using a diary card for a period of seven days after each vaccination. Additional data on adverse events occurring outside this period were collected until 18 months of age. Vaccination was postponed if the infant had an axillary temperature of ≥38°C or had received antibiotic treatment within the previous seven days. Erythema at the injection site was the most commonly reported local reaction followed by induration (91.4% and 53.6%, respectively); overall, a greater proportion of infants experienced local reactions after the fourth dose of 4CMenB vaccine compared to earlier doses (e.g., 70.5% versus 46%-50%, for induration). Irritability, a change in eating habits and sleepiness were the most common solicited systemic reactions at 68.3%, 25.5% and 22.9%, respectively. The proportion of systemic reactions was similar after each dose of 4CMenB vaccine, with the exception of sleepiness after the first dose (64% versus 27.5–44% after doses 2-4) and fever ≥38°C after the first dose (18% versus 4.5–8% after doses 2-4). In total, 18 serious adverse events were reported: 12 cases of bacterial or viral infections and one case each of transient reactive arthritis of the knee, hydrocele, deafness (presumed congenital), pyrexia, wheezing and purpura. The case of transient arthritis of the knee, which occurred one month after vaccination with the comparator vaccine (meningococcal B recombinant vaccine without the OMV component), was judged to be possibly related to the vaccine by study investigators. Timing of the other serious adverse events in relationship to vaccination was not provided. In summary, the most frequently reported local or systemic reactions consisted of erythema, induration and irritability (54–91%, all doses combined). Fever (axillary temperature ≥38°C) occurred in 9% (all doses combined) and was most common after the first dose (18% versus 5–8% after doses 2 to 4). None of the 18 serious adverse events were attributed to 4CMenB vaccine by study investigators, however one (a case of transient arthritis of the knee) was judged to be possibly related to a recombinant meningococcal B (rMenB) vaccine, which is 4CMenB vaccine without the OMV component.

In the *Snape et al* (2010)(25) single- (parent/guardian) blind trial, 30 infants were randomized to receive three doses of 4CMenB vaccine given at 6 to 8 months of age, 60 days later and 12 months of age. Menitorix® was also administered at 12 months of age. Parents recorded their child's local reactions, solicited systemic reactions, axillary temperature and use of analgesic and antipyretic medication daily for seven days after each vaccination. Any adverse event that required a physician's visit within 30 days of study vaccine administration was documented, and additional data on serious adverse events were collected by study personnel through a phone call to parents six months after the final study vaccine. Proportions of local and solicited systemic reactions following each dose of 4CMenB vaccine were comparable. Similar to the finding of *Findlow et al* (2010), the most commonly reported local reactions were erythema and induration (90.6% and 61.2%, respectively) and the top three most common solicited systemic reactions were irritability, sleepiness and a change in eating habits (57.6%, 27.1% and 23.5%, respectively). The probability of fever >38°C was 10.0% after the first dose, 10.7% after the second dose and 3.7% after the third dose. One infant had a fever of >39.5°C following the third dose of 4CMenB vaccine, and one case of febrile convulsion associated with tonsillitis was reported five days after the third dose of 4CMenB vaccine. The following five serious adverse events were reported following vaccination with the comparator vaccine (meningococcal B recombinant vaccine without the OMV component): two cases of cellulitis (not related to immunization site), and one case each of wheezing, croup and gastroenteritis, none of which were attributed to the study vaccine by study investigators. In summary, erythema, induration and irritability were each reported in 58–91% of participants (all doses combined). Fever (axillary temperature >38°C) occurred in 8% (all doses combined) and was more common after the first and second dose (10% and 11% vs. 4% after dose 3). One case each of fever (>39.5°C) and febrile convulsion associated with tonsillitis were reported following 4CMenB vaccine.

The *Prymula et al* (2011)(26) study measured rates of fever among 367 infants following vaccination with 4CMenB and Infanrix-hexa® and Prevenar® at 2, 3 and 4 months of age, when given with or without three doses of prophylactic paracetamol (10-15 mg/kg per dose). The safety outcome was rectal temperature, measured for a period of seven days after vaccination. Overall, the proportion of infants with fever was highest following the first dose of 4CMenB vaccine and decreased with each successive dose. After the first dose of 4CMenB vaccine, 51% of infants had fever (≥38.5°C) compared to 25% of infants who were given paracetamol (for all doses combined, 43.3% vs. 18.3%). For ≥39.5°C, these proportions were 5% compared to 1% of infants given paracetamol (for all doses combined, 4% vs. 1%). In summary, the proportion of infants with fever (rectal temperature ≥38.5°C) following vaccination with 4CMenB plus Infanrix-hexa® and Prevenar® was reduced from 43% to 18% (all doses combined) when infants were given prophylactic paracetamol.

In the open label trial conducted in Europe, *Gossger et al* (2012)(22) compared the safety of three different 4CMenB vaccination schedules in 1571 infants: concomitant administration of 4CMenB vaccine with Infanrix-hexa® and Prevenar® at either 2, 4 and 6 months of age or 2, 3 and 4 months of age; or separate administration of 4CMenB vaccine at 2, 4 and 6 months of age, with Infanrix-hexa® and Prevenar® given at 3, 5 and 7 months of age. A control group of 314 infants received only Infanrix-hexa® and Prevenar® at 2, 3 and 4 months of age. Safety analyses used a modified ITT population consisting of those who received at least one dose of vaccine and provided post-baseline safety data (concomitant 2, 4, 6 schedule, n=602-624; separate 2, 4, 6 and 3, 5, 7 schedule, n=601-626; concomitant 2, 3, 4 schedule, n=310-317; and control group, n=304-311). Solicited local and systemic reactions including fever (axillary temperature) were recorded by parents of the participants for a period of seven days after each vaccination. The recording of adverse events was enhanced through telephone contact in the week after study vaccination. Safety follow-ups were completed 6 months after the last dose of 4CMenB vaccine or at age 10 months in the control group. The probabilities of erythema, induration and swelling at the injection site were similar among the three different 4CMenB vaccine schedules. However probabilities of pain and systemic reactions increased when 4CMenB vaccine was given concomitantly with Infanrix-hexa® and Prevenar® at 2, 4, 6 or 2, 3, 4 months of age (9.5%-73.5%, concomitant groups; 6.0%-59.1%, separate group; 3.3–51.6%, control group). Additionally, higher probabilities of fever ≥38°C were observed in the concomitant groups (53.4% and 57.8%) compared to the separate group (35.0%) and control group

(29.8%). For fever ≥39°C, these proportions were 9.5% and 12.0% in the concomitant groups compared to 6.0% in the group that received 4CMenB vaccine on separate occasions from routine vaccines, and 3.3% in the control group.

A total of 166 serious adverse events were reported by 158 infants, of whom a majority, 63 infants, received the concomitant 2, 4, 6 month schedule. Twenty of the 166 serious adverse events were attributed to 4CMenB vaccine or routine vaccines by the study investigators based on temporal relationship and biological plausibility criteria, and 19 of 20 were described in the paper. Of these 19 events, 6 were infants who received medical attention for fever within 2 days of receiving 4CMenB vaccine. One case of febrile seizure occurred 2 days after the second dose of 4CMenB vaccine given separate from routine vaccines and 3 cases of seizure following each of: 4CMenB vaccine given separate from routine vaccines; routine vaccination in the separate group; and, vaccination in the concomitant 2, 3, 4 month schedule group, respectively. There were two cases of hypotonic hyporesponsive episode, of which one case (onset within 12 hours of concomitant 4CMenB vaccine and routine vaccines) was attributed to 4CMenB vaccine and the other case (onset within 6 hours of routine vaccines in the group who got routine vaccines on separate occasions) to routine vaccination. There were two cases of Kawasaki disease, one of which was considered possibly related to 4CMenB vaccine by an independent expert panel. One case each of aseptic meningitis, retinal dystrophy (believed to be congenital), transient synovitis of right hip, transient hearing loss (noted by a parent) and transient apnea occurred following concomitant vaccination and were considered possibly related to 4CMenB vaccine or routine vaccines. Thirteen infants receiving 4CMenB vaccine withdrew from the study because of an adverse event, compared to none in the control group. In summary, the probabilities of local reactions at the injection site were similar among the three different 4CMenB vaccine schedules. However, higher proportions of pain and systemic reactions, including fever, were observed when 4CMenB vaccine was given concomitantly with Infanrix-hexa® and Prevenar®, compared to separately. Fever ≥38°C was reported in up to 57.8% (12.0% ≥39°C) of infants in the concomitant groups, compared to 35.0% (6.0% ≥39°C) in the separate group and 29.8% (3.3% ≥ 39°C) in the control group. Medically attended fever was reported in 6 infants. Serious adverse events following vaccination were reported most frequently in the concomitant 2, 4, 6 month group. Overall, 20 of 166 serious adverse events were attributed to 4CMenB vaccine or routine vaccines by the study investigators. An equal proportion of neurologic events (seizure, febrile seizure and hypotonic hyporesponsive episode), were attributed to 4CMenB vaccine as were attributed to routine vaccines.

Safety of 4CMenB vaccine was assessed in the large phase III trial conducted by *Vesikari et al* (2013)(35), summarized above in the immunogenicity section. Data were initially obtained from a conference poster by *Esposito et al* (2010)(40) but have since been updated based on the published manuscript. The authors assessed the safety of 4CMenB vaccine with routine vaccines Infanrix-hexa™ (GlaxoSmithKline) and Prevenar™ (Pfizer) in 3630 infants in Europe. Infants in the open label (safety) subset were randomized to receive one of three lots of 4CMenB vaccine given with routine vaccines at 2, 4 and 6 months of age (n=1966), or routine vaccines alone at 2, 4 and 6 months of age (n=659). Infants in the observer-blind subset were randomized to receive either 4CMenB vaccine (n=493) or Menjugate™ (n=470), given at 2, 4 and 6 months of age with routine infant vaccines. Children were monitored for half an hour after vaccination. Solicited local reactions at the injection site and solicited systemic reactions including medically attended fever were recorded for seven days following vaccination. Other (spontaneously reported) adverse events were evaluated throughout the study and infants were followed up to 12 months of age.

In both subsets, probabilities of local and systemic reactions (excluding fever) were higher among infants who received 4CMenB vaccine, given concurrently with infant routine vaccines, compared to those who did not receive 4CMenB vaccine. Only local and systemic reactions in the observer-blind cohort, all doses combined, are summarized in Table 5, based on *Esposito et al* (2010)(40) but pooled safety data is presented, in text, here. The researchers state that safety data were pooled from the open-label and observer-blind cohorts for their publication(35) because reactogenicity profiles were similar in these two groups. Likewise, reactogenicity did not differ across doses and the authors reported safety information for all doses, combined. Tenderness was the most common local reaction and was experienced by 87% of 2147 infants following 4CMenB vaccine, of which 29% were severe (defined as "cried when limb moved"), compared to 55% (3.5% severe) in the Menjugate™ plus routine vaccines group. Erythema, induration and swelling after 4CMenB vaccine were each reported in 47-83 % of infants. The most common systemic reactions following 4CMenB vaccination were unusual crying [85% vs. 72% (352/490) after Menjugate™], irritability (93% vs. 76% after Menjugate™) and sleepiness (87% vs. 72%).

A majority of infant participants [65.3% (1612/2468)] in the observer-blind and open label cohorts combined experienced rectal temperatures of ≥38.5°C within the first six hours following 4CMenB vaccine. The frequency of fever following 4CMenB vaccination in both cohorts combined peaked at six hours after each dose. The proportion of participants with fever in this temperature range decreased with each successive dose. Fewer participants experienced fever >39°C and this proportion also decreased with each successive dose. Ninety-three percent reported using analgesics or antipyretics after one of the 2, 4, or 6 month doses. When parents of infants in the open-label subset were informed about potential fever events after vaccination (*personal communication with Novartis*), the rate of medically attended fever among infants who received 4CMenB vaccine with routine vaccines was lower in the open-label subset (n=28/1966 or 1.42%) than the observer-blind subset (n=26/493 or 5.27%). Details on whether parents were counseled to prophylactically administer anti-pyretic is unclear.

Other adverse event profiles were reported as being similar between lots of 4CMenB vaccine. According to *Esposito et al*'s (2010)(40) poster, the most common other adverse events in infants receiving 4CMenB vaccine with Infanrix-hexa™ and Prevenar™ were reported as otitis media (18%), upper respiratory tract infection (16%), bronchitis (13%) and nasopharyngitis (10%), and were “generally considered not related to the study vaccine” by study investigators. Serious adverse events were reported in 8% of infants receiving 4CMenB vaccine with routine vaccines, 8% receiving routine vaccines alone, and 6% receiving Menjugate™ with routine vaccines, although the details of these serious adverse events were not provided and were listed as follows: pyrexia, cerebral palsy, microcephaly, irritability, diarrhea and upper respiratory tract infection, vaccine reaction (fever, diarrhea, loss of appetite, swelling at injection site), arthritis, convulsion with fever, varicella, tremor and seizure. In *Vesikari et al* (2013)(35), details are provided regarding seizures and Kawasaki disease. Two seizures occurred in infants on the same day as the first dose of 4CMenB vaccine and routine vaccines. These were accompanied by fever but seizure-like movements were limited to one or two limbs. The authors considered these possibly related to 4CMenB vaccine. Two cases of febrile seizures in infants occurred within 24 hours of the second dose of 4CMenB (with routine vaccines) and were assessed by the study authors to be probably related to 4CMenB vaccine. Of note, one of these children had underlying renal disease, "neurological pathologies" and developmental delay and went on to have another febrile seizure after withdrawing from the study. The authors reported three confirmed cases of Kawasaki disease and one unconfirmed case (assessed by an independent expert panel). One of the confirmed cases occurred in a child who was not immunized with 4CMenB vaccine. The other three occurred 3, 7, and 14 weeks after vaccination during the three dose infant series. Overall, there were 17 serious adverse events (among 15 children), all but one of which were in the 4CMenB group, which the investigators considered vaccine related and all resolved prior to completion of the study, with the exception of the case of microcephaly (who had associated blindness). Less than 1% of participants discontinued the study due to an adverse event. In summary, solicited local reactions were recorded in 36% (swelling) up to 86% (tenderness) of infants during the 7-day period following vaccination with 4CMenB and Infanrix-hexa™ and Prevenar™, and solicited systemic reactions were reported in 10% (rash) up to 91% (unusual crying) of infants. Up to 60% of infants experienced fever ≥38.5°C and up to 86% had recorded use of analgesics or antipyretics. Further, up to 5.3% of infants received medical attention for fever during the 7-day period following vaccination with 4CMenB and routine vaccines, compared to up to 2.8% of infants who did not receive 4CMenB vaccine. Finally, serious adverse events were reported in a similar percentage (8%) of infants receiving 4CMenB vaccine with routine vaccines versus routine vaccines alone, but this percentage was lower in infants receiving Menjugate™ with routine vaccines (6%).

In the fourth/booster dose extension of *Vesikari et al*'s (2013)(35) phase III open label study described above (data initially extracted from a conference poster by *Vesikari et al* (2011)(28) and subsequently updated based on the publication), 1555 children previously vaccinated with three doses of 4CMenB vaccine in infancy (according to a 2, 4, 6 primary immunization schedule) were randomized to receive a booster dose at 12 months of age, with Priorix-Tetra™ (GlaxoSmithKline) at either 12 month of age (*concomitant* group, n=766) or 13 months of age (*separate* group, n=789). Solicited local and systemic reactions were recorded by parents for seven days after each vaccination using diary cards, while other adverse events were recorded for 28 days. We report data on local and systemic reactions from the conference poster as the data appear to have been reversed in the paper based on number of participants per group. Rates of all local reactions, as well as rates of local severe reactions, at the injection site after the booster dose of 4CMenB vaccine were similar in both groups, with tenderness (70%, in both groups) and erythema (67% in the separate group and 65.5% in the concomitant group) being the most common. In both groups, the most common systemic reactions were irritability (68% separate vs. 72.5% concomitant) and sleepiness (44.5% separate vs. 46.5% concomitant) and fever ≥38°C (40% separate vs. 48% concomitant, data on file with Novartis). Two serious adverse events were mentioned and attributed to vaccination: one case each of febrile convulsion and one of pyrexia (2 days after vaccination), both in the concomitant group. The febrile seizure occurred 9 days after concomitant 4CMenB vaccine and MMRV and was attributed to MMRV. Eight other febrile seizures occurred between 9 days and 6 months of 4CMenB 12 month booster and were felt not to be due to 4CMenB vaccine. In summary, while probabilities of local reactions were similar, the probabilities of systemic reactions, including fever (≥38°C), were generally higher in the group that received 4CMenB vaccine with concomitant Priorix-Tetra™ compared to 4CMenB vaccine alone.

Children 12 to 24 months of age

Safety of 4CMenB vaccine initiated in children aged 12 to 24 months was measured in approximately 1600 healthy participants in two clinical trials, both conducted in Europe.(13),(34)

In the *Findlow et al* (2010)(13) study, 23 infants were randomized to receive a single dose of 4CMenB vaccine at 12 months of age with UK infant vaccines. As described in the infant section above, routine vaccines were administered as follows: Pediacel® at 2, 3, 4 months of age; Prevenar® at 2, 4, 13 months of age; Menjugate® at 3, 5 months of age; Menitorix® at 12 months of age; and Priorix® at 13 months of age. Vaccination was postponed if the infant had an axillary temperature of ≥38°C or had received antibiotic treatment within the previous seven days. Erythema and induration were the most common local reactions and were reported by 100% and 83%, respectively. Tenderness was experienced by 30% of children; however local severe tenderness occurred in 13.5%. Irritability, sleepiness and a change in eating habits were the three most common solicited systemic reactions (57%, 43% and 26.5%, respectively), and 17% experienced a fever of ≥38°C. There were no serious adverse events attributed to 4CMenB vaccine or routine vaccines among these 12-month-olds (n=23) immunized with one dose of 4CMenB vaccine.

The open label phase III trial, reported by *Vesikari et al* (2011)(28) and previously summarized in the infant safety section, also assessed the safety of 4CMenB vaccine when administered as a 2-dose series given to healthy toddlers. In this study by *Prymula, Vesikari, Esposito et al* (2011)(34), which is an extension of the *Esposito et al* (2010)(40) trial described above, 402 children in five European countries who did not previously receive 4CMenB vaccine with routine vaccines at 2, 4, and 6 months of age, were randomized to receive two doses of 4CMenB vaccine given at either 12 and 14 months of age (n=117) or 13 and 15 months of age (n=285). Both groups also received MMRV (Priorix-Tetra™, GlaxoSmithKline) at 12 months of age. All participants were included in the safety analysis except for one child in the group receiving Priorix-Tetra™ at 12 months of age and 4CMenB vaccine at 13 and 15 months of age, who was withdrawn after receiving Priorix-Tetra™. Solicited local and systemic reactions as well as other adverse events were recorded for seven days after each vaccination, and medically attended serious adverse events were recorded throughout the study (total duration of study not stated on conference poster). Temperature was analyzed for day 1 to day 4 after each 4CMenB vaccination, and day 5 to day 28 after each Priorix-Tetra™ vaccination.

Similar percentages of tenderness and swelling at the injection site were observed when 4CMenB vaccine was given with or without Priorix-Tetra™. However, after the first dose of 4CMenB vaccine, 70% and 52% of children had erythema and induration, respectively, when given 4CMenB vaccine with Priorix-Tetra™, compared to 62.25% and 40% of children that received 4CMenB vaccine alone. Rates of systemic reactions after the first dose were also higher among children that received 4CMenB vaccine with

Priorix-Tetra™ with the exception of vomiting which was slightly higher among children that received 4CMenB vaccine alone. A slightly higher proportion of children experienced fever (≥38°C) 1 to 4 days after receiving their first dose of 4CMenB vaccine when given with concomitant Priorix-Tetra™ compared to without (37% vs. 35.5%). The proportion with fever 1 to 4 days after the second dose of 4CMenB vaccine was 40% and 34.5% in the concomitant and non-concomitant groups, respectively. The probability of fever (≥38°C) occurring 5 to 28 days following Priorix-Tetra™ (given at 12 months of age) was 44% in the concomitant group and 53% in the non-concomitant group. No participants withdrew from the study due to vaccine-related serious adverse events, although one subject withdrew after the first dose of 4CMenB vaccine (given at 13 months of age) with a diagnosis of asthma. Two cases of febrile seizure were reported, occurring 31 and 53 days after the second dose of 4CMenB vaccine in the concomitant and separate groups, respectively. One serious adverse event, reported 4 ½ months after vaccination, was considered a case of Kawasaki disease by an independent expert panel and unrelated to vaccination.

Children 2 to 10 years of age

The safety of 4CMenB vaccine initiated in children aged 2 to 10 years has been studied in 84 participants. As noted in the immunogenicity section, the "control" groups in extension of *Findlow et al* (2010)(13), for which safety was reported by *Saroey et al* (2012)(30) and *Martin et al* (2012)(41), and in the extension of *Snape et al* (2010)(25) [safety presented by *Phillip et al* (2012)(32) and *Martin et al* (2012)(41)] were children previously unimmunized with 4CMenB vaccine who were given the vaccine at 40 and 42 months of life. The "experimental" groups in these two studies had completed infants series of 4CMenB vaccine [2, 4, 6, 12 mos or 12 mos in *Findlow et al* (2010)(13) and 6, 8, 12 mos in *Snape et al* (2010)(25)] and were given a single booster at 40 months of life. The safety of this booster dose, examined in fewer than 50 children, will be discussed here as well.

Regarding 4CMenB naïve children, *Saroey et al* (2012)(30) and *Martin et al* (2012)(41) present the reactogenicity of 4CMenB vaccine in 43 children who were vaccinated at 40 and 42 months of life. In this study, parents recorded adverse events on a diary card and took children's temperatures daily in the week following immunization. Definitions were provided for severe local reactions (severe tenderness defined as inability to perform daily activities and severe erthythema, swelling, and induration defined as ≥ 50mm) but not for severe systemic reactions. Local pain and erythema were very common (occurring in ≥85% of participants at each dose) and severe pain was reported by 20% after the first dose and 15% after the second dose. Induration and swelling occurred in ≤50% of participants at each dose. The most common systemic reaction was irritability (75% after the first dose and 58% after the second dose). Arthralgia was reported by 31% of children after the first dose (8% severe) and 21% after the second dose (6% severe). Fever ≥38°C occurred in 10% and 12% of children after the first and second doses, respectively. There were no temperatures ≥39°C after the first dose but fever ≥39°C occurred in 4% after the second dose (≥40°C in 2%). The only serious adverse event reported in this study was an episode of cervical adenitis which was considered unrelated to 4CMenB vaccine.

Similarly, *Philip et al* (2012)(32) and *Martin et al* (2012)(41) reported on the safety of 4CMenB vaccine given to 41 children at 40 and 42 months of age, also through parental completion of diary cards and temperature measurement for one week after immunization and with the same definitions of severe reactions as above. Local reactions occurred at frequencies similar to that in the study described in the preceding paragraph. Regarding systemic reactogenicity, no arthralgia was reported and irritability was the most common systemic reaction (59% after the first dose, 68% after the third dose), followed by sleepiness (52% after the first dose and 45% after the second dose; 7% severe after both doses). There were two serious adverse events in this group of vaccines. One was a case of meningoencephalitis reported to be unrelated to 4CMenB vaccine (no further information provided) and the second was a febrile seizure that occurred 8 hours after the second dose of 4CMenB vaccine accompanied by a temperature of 39.3°C which the authors describe as possibly related to 4CMenB vaccine.

The safety of a booster dose(s) of 4CMenB vaccine at 40 months of life is similar to that of primary immunization in this age group. *Saroey et al* (2012)(30) and *Martin et al* (2012)(41) describe the safety of 4CMenB vaccine boosters in 19 children who had received the vaccine at 2, 4, 6, and 12 months and 8 children who were only vaccinated at 12 months. The latter group received a single dose at 40 months of age and the former two doses at 40 and 42 months of age. Methods were as described above. Local reactions were very common, especially pain and erythema, in both groups. The proportions who experienced systemic reactions were similar in the two groups and irritability and sleepiness were most frequently reported (e.g. irritability occurred in 52% of the children who got a single booster and in 63% of children after both doses in the two-dose booster group). Arthralgia occurred in 33% (4% severe) of the 19 children who were given a single booster at 40 months of life after a primary 4CMenB vaccine series at 2, 4, 6, and 12 months. Likewise, arthralgia occurred in 24% after the first booster dose and 25% (12% severe) after the second booster dose among the 8 children who had previously received only a single dose of 4CMenB vaccine when they were 12 months old. The authors did not report any serious adverse event in these two groups.

Philip et al (2012)(32) and *Martin et al* (2012)(41) ministration of a single 4CMenB booster to 14 children who were 40 months old and had received three doses of the vaccine at 6, 8, and 12 months of life in *Snape et al* (2010)(25) study of 4CMenB in late infancy. As noted previously, parents recorded solicited and unsolicited reactions on a diary card and measured children's temperatures daily for 7 days after immunization and there were no definitions noted on posters for severe systemic reactions. All of these children experienced pain (15% severe) and erythema after immunization. Irritability occurred in 80%, sleepiness in 50% and decreased appetite in 35%. Seven percent had fever ≥38°C. There were no reports of arthralgia in this small group.

Adolescents 11 to 17 years of age

The large observer-blind phase IIB/III "placebo-controlled" trial by *Santolaya et al* (2012)(21) in Chile assessed the safety of one-, two- or three-dose schedules of 4CMenB vaccine in adolescents aged 11 to 17 years. A total of 1631 participants were randomized to receive 4CMenB vaccine or an aluminum-hydroxide control, as described above. The safety analyses included all participants and were descriptive only, with no pre-defined statistical criteria. Ad hoc analyses using chi square test were performed by the study authors to compare differences between 4CMenB vaccine and the aluminum-hydroxide control. Solicited local and systemic reactions were recorded at

30 minutes and within 7 days post-injection at 0, 1, 2 and 6 months. Severe pain and severe systemic reactions were defined as interference with normal activities. The occurrence of other adverse events and serious adverse events, including medically attended events, were recorded throughout the study. The exact study duration was not stated, but there was a serious adverse event reported 198 days after a 2-month injection, suggesting some period of observation beyond 6 months. The authors report the cumulative reactions for all doses of 4CMenB vaccine or placebo (all schedules combined). An independent data monitoring committee provided guidance for interpretation of safety outcomes.

Among adolescents in this study, 4CMenB vaccine was associated with a greater proportion of solicited local reactions at the injection site compared to the aluminum-hydroxide control. Proportions of local reactions after 4CMenB vaccine were similar after each dose, with a slight decrease in percentages after the second and third dose (90–91% and 87% of adolescents after the second and third doses, respectively, compared to 93–95% after the first dose). A similar decrease in proportions of local reactions was reported in adolescents who received three control injections (92% at month 0, 84% at month 1 and 78% at month 2). Pain was the most common local reaction, and was reported after 86% of 4CMenB vaccine injections compared with 60% of control injections; of these, 17% of 4CMenB vaccine injections compared with 4% of control injections were described as severe pain. Similarly, 4CMenB vaccine was associated with a greater proportion of systemic reactions, the most common of which included: malaise after 51% of 4CMenB vaccine doses (compared with 30% of control injections; $p<0.0001$), myalgia after 43% of 4CMenB vaccine doses (compared with 23.5% of control injections; p-value not provided) and headache after 42% of 4CMenB vaccine doses (compared with 27% of control injections; $p<0.0001$). School absenteeism was reported after 12% of 4CMenB vaccine injections compared with 4% of control injections. Fever, defined as an axillary temperature of ≥38°C, was reported after 4% (n=123/3329 doses) of 4CMenB vaccine injections compared with 2% (n=44/2738 doses) of control injections ($p<0.0001$). There was no significant difference in the proportion of reported fevers of ≥39°C in 4CMenB vaccine recipients (n=20) versus control recipients (n=8; $p=0.0689$). Among participants who reported whether or not they sought medical attention for fever, 4 (0.3%) of 1480 4CMenB vaccine recipients and 2 (0.2%) of 1290 control recipients sought medical attention. A significantly higher proportion of 4CMenB vaccine recipients reported using antipyretic drugs during the trial: 61 (4%) of 1461 4CMenB vaccine recipients vs. 22 (3%) of 689 control recipients (p<0.0002), who reported whether or not they used antipyretic drugs.

According to the authors, serious adverse events reported by participants following vaccination with 4CMenB vaccine were juvenile arthritis (n=2), appendicitis (n=4), Shigella infection (n=1), drug-related toxic effects (n=1), pneumococcal meningitis (n=1), asthmatic crisis (n=1), vasovagal reaction and convulsion (n=1) and death (n=2). All of the above were judged to be unrelated to 4CMenB vaccine by study authors, with the exception of juvenile arthritis. Both juvenile arthritis events were reported following the third dose of 4CMenB vaccine in a 0, 1, and 2 month schedule with onset occurring 170 days and 198 days after vaccination, respectively. These two cases were considered possibly and probably, respectively, related to 4CMenB vaccine. In comparison, 26% (n=15/57) of control recipients reported an event that was attributed to the aluminum-hydroxide control. Two participants prematurely withdrew from the study because of serious adverse events (one with juvenile arthritis and another with vasovagal reaction and convulsion).

In summary, local reactions were reported by 39–86% of adolescents and systemic reactions, excluding fever, by 15–51% (all doses combined). Twelve percent stayed home as a result of 4CMenB vaccination. Fever (axillary temperature of ≥38°C) was significantly higher following 4CMenB vaccine compared to control (4% vs. 2%, p<0.0001), as was the proportion that reported use of antipyretic drugs following 4CMenB vaccine (4% vs. 2%, p<0.0002). Medical attention was sought by 0.27% adolescents following 4CMenB vaccination. Serious adverse events reported by participants following vaccination with 4CMenB vaccine included juvenile arthritis (n=2), vasovagal reaction and convulsion (n=1) and death (n=2).

Adults 18 to 55 years of age

In the phase II open label study by *Kimura, Toneatto, Kleinschmidt et al* (2011)(38), conducted in Germany and Italy, 54 healthy laboratory workers aged 18 to 50 years (mean age 31.8 ± 6.1 SD) were enrolled and given three doses of 4CMenB vaccine at 0, 2 and 6 months. At 7 months, 41 participants also received MenACWY-CRM (Menveo®, Novartis). Solicited local and systemic reactions, temperature and medication use plus other unspecified adverse events were recorded 30 minutes and 7 days after each dose; while medically attended adverse events, adverse events leading to withdrawal from study and serious adverse events were recorded throughout the study until 6 months after the last dose of study vaccine. Severe local or systemic reactions were defined as an inability to perform daily activities. Overall, local pain was reported by 98.1% of participants, of which 15.5% reported that they were unable to perform daily activities due to pain. Induration and erythema were reported by 49.0% (0% severe) and 47.1% (0% severe) of participants, respectively. Systemic reactions and severe systemic reactions were reported as follows: malaise 38.1% (3.9% severe), myalgia 37.4% (8.4% severe), headache 31.9% (1.3% severe), arthralgia 27.1% (1.9% severe) and nausea 13.5% (1.3% severe). Nine percent stayed home. The study reported fever ≥38°C in 1.9% and pyrexia (undefined) in 2.6%. Further, 14.2% reported using an analgesic or antipyretic. The study authors also presented proportions of local and systemic reactions after each dose and while there seemed to be a trend toward increased reactogenicity after each subsequent dose, no statistical analysis was performed. No serious adverse events or death were reported. In addition to solicited local and systemic reactions, 24 (45%) participants experienced at least one "adverse event" and 7 (13%) were possibly related to the vaccination (details not provided). Only the most common reported adverse events were reported in the study: 6 cases of nasopharyngitis following 4CMenB vaccine (three cases after dose 2 and three cases after dose 3); and 3 cases of rhinitis. One participant withdrew due to syncope and another due to nasopharyngitis, neither of which were considered related to the study vaccines by study investigators. In summary, local reactions (pain, induration and erythema) were reported in 47.1–98.1% of participants. Systemic reactions were reported in up to 38.1%, with fever/pyrexia occurring in up to 2.6% of participants. No serious adverse events were reported. Forty-five percent experienced at least one "adverse event", of which 13% were possibly related to the vaccine.

In *Findlow et al*'s (2012)(39) phase II study of 4CMenB vaccine in 38 UK laboratory workers, where 4CMenB vaccine was given at 0, 3 and 6 months, the first dose accompanied by Menveo® safety was assessed during the seven days following each immunization. Participants recorded local and systemic reactions on a diary card. Nearly all subjects reported pain at 4CMenB injection site, with 3% reporting severe pain with the second dose. Induration at 4CMenB injection site was noted by 41–51% of participants, depending on dose. Three percent experienced severe induration after the second dose. Twenty-two to 42% reported erythema at 4CMenB vaccine site (3% severe at third dose). Of note, 4CMenB vaccine local reactogenicity was more marked than that of Menveo®. As well, 4CMenB vaccine local reactogenicity was greatest after the third dose. On the other hand, systemic reactogenicity was greatest after the first dose, which was given concomitantly with Menveo®. Twenty-five percent experienced nausea and 38% had headache after the first dose whereas after the second dose 18% had nausea and headache. With the third dose 12% had nausea and 17% had headache. One participant reported fever after the first and second vaccination and another reported fever only after the second. The authors state there were 13 adverse events during the study period and nine of these were considered possibly related or related to 4CMenB vaccine. These nine adverse events consisted of eight injection site reactions and an illness consisting of myalgia and nausea that occurred three days after the second dose of 4CMenB vaccine.

Adults >55 years of age

There are currently no studies of the safety and reactogenicity of 4CMenB vaccine in adults over the age of 55 years.

III.2.4. CRITICAL APPRAISAL OF 4CMENB VACCINE STUDIES

Grading of evidence for the 4CMenB vaccine trials was based on data available from published studies as well as additional methodological information provided by the manufacturer. Final decision following comprehensive quality assessment was made in consultation with Meningococcal B Pilot Project Task Group members.

III.2.5. EFFICACY AND EFFECTIVENESS OF NZ-OMV VACCINE

No large randomized controlled efficacy (phase III) trials of the NZ-OMV vaccine (MeNZB™, Novartis, formerly Chiron) vaccine were undertaken prior to its approval for use to help quell an ongoing outbreak of serogroup B:4:P1.4 IMD in that country. There was comprehensive meningococcal surveillance in New Zealand (population 4.4 million, 2012) following introduction of the vaccine campaign in 2004, and four primary post-licensure publications addressing the effectiveness of MeNZB™ vaccine against the predominant specific IMD phenotype were identified by the search strategy.(42),(43),(44),(45) The findings of these studies are summarized in Table 6.

McNicholas et al (2008)(42) compared rates of the epidemic strain of serogroup B IMD infection two years prior to the introduction of NZ-OMV vaccine to two years after its introduction, with 2004, the year of program implementation treated as a 'wash out' and excluded from calculations. Overall, the rate among New Zealanders less than age 20 years decreased among all ethnic groups: 2002-03: Pacific 35.6 per 100 000, Māori 28.2 per 100 000, and European/other 11.3per 100 000; 2005-06: Pacific 11.4 per 100 000, Māori 8.8 per 100 000, and European/other 3.6 per 100 000. It is important to note that rates of disease as discussed in *McNicholas et al* (2008)(46) had been on the decline since 2000, as such, descriptive epidemiology alone does not prove NZ-OMV vaccine impact.

Vaccine effectiveness (VE) was estimated in the three remaining papers by the same research group. Using a generalized estimating equation controlling for region-specific disease rates, age, ethnicity, socioeconomic status, disease progression over time and seasonality, *Kelly et al* (2007)(43) found that unimmunized individuals were at nearly 4 times the risk of epidemic strain IMD versus immunized individuals (relative risk, RR=3.7; $p<0.0001$), during the period 2001 to 2006 (vaccine program initiated in 2004 for all New Zealanders aged 6 months to 19 years). Using this RR estimate, the study authors calculated the VE to be 73% (95% CI: 52, 85) (VE=1-1/RR), and the model predicted that an additional 54 (95% CI: 22, 115) cases of epidemic serogroup B IMD cases were prevented by the vaccine.

Arnold et al (2011)(44), from the same research group, has recently published a more conservative estimate of NZ-OMV VE. The methodology was similar but they also accounted for residual confounding by modeling the VE of NZ-OMV vaccine against invasive pneumococcal disease (IPD) which has no biologic plausibility and should be zero. Depending on the assumptions in the regression model, VE ranged from 53.3% (95% CI: 25, 71) to 76.5% (95% CI: 62, 85) over an average duration of follow-up of 3.2 years. The most conservative estimate was derived from a model that controlled for the VE against IPD suggesting that residual confounding remained. The authors propose that because the immunization campaign was voluntary, those of lower socioeconomic status may have been less likely to be immunized (due to missed opportunities) and at higher risk of disease (due to over-crowding) and that the social deprivation scale used in the statistical model may not have adequately captured these issues. There may be other, unknown residual confounders as well.

Lastly, *Galloway et al* (2009)(45) estimated VE in a prospective population-based cohort study of all children aged 6 months to <5 years at the time the NZ-OMV vaccine became available. Cases were defined as those with laboratory-confirmed epidemic strain IMD. The vaccinated cohort was subtracted from Statistics New Zealand population estimates for 2004 to get an estimate of the number of unvaccinated children in each district health board. 160 870 of 258 421 (62.3%) children in the vaccinated cohort received at least three doses given at 6-week intervals (fully vaccinated) during the 24 month follow-up period whereas 90.5% received one, two or three doses (233 906/258 421). Children in the vaccinated cohort who received one or two doses of NZ-OMV were referred to as partially vaccinated (73036/258 421 [28.2%]). Twelve of 28 (42.9%) laboratory confirmed epidemic strain cases were fully vaccinated prior to disease onset. Fully vaccinated children were five times less likely to be infected with epidemic strain meningococcal disease than unvaccinated children, corresponding to an estimated VE of 80.0% (95% CI: 52.5, 91.6) for children aged 6 months to under 5 years. VE for partial vaccination (receipt of one or two doses) was 71.1% (95% CI: 22.3, 89.2).

In a separate analysis in this paper, 89 776 of 143 265 (62.7%) children aged 6 months to under 3 years were fully vaccinated and 40 235 (28.1%) were partially vaccinated. Eight of 22 (36.4%) laboratory confirmed epidemic strain cases in this young age group, received three properly spaced doses prior to disease onset. Fully vaccinated children in this age group were six times less likely to be infected with the epidemic strain IMD compared to unvaccinated children, corresponding to an estimated VE of 84% (95% CI: 59.4, 94.3). VE for partial vaccination was 71.4% (95% CI: 17.6, 90.1).

VE estimates for the first 12 months following eligibility to complete a full vaccination series were 81.5% (95% CI: 36.9, 94.6) for children aged 6 months to <5 years and 89.2% (95% CI: 46.3, 97.8) for children aged 6 months to <3 year. However, for the second 12-month period (months 13 to 24), VE estimates were much lower at 33.0% (95% CI: -215.7, 85.8) and 50.2% (95% CI: -146.5, 90.0) for the two age groups, respectively.(45)

Based on this literature, the NZ-OMV VE is between 33–84%, depending on age cohort, number of doses, modelling methods and time from vaccination (i.e., waning immunity). No papers explicitly described herd effects, however rates of disease dropped in the entire population.

III.2.6. IMMUNOGENICITY OF NZ-OMV VACCINE

See Appendix 2.

III.2.7. SAFETY OF NZ-OMV VACCINE

See Appendix 2.

III.2.8. POST-LICENSURE SURVEILLANCE OF NZ-OMV VACCINE

As part of the secondary inclusion criteria of the literature review, four post-licensure studies of the safety of NZ-OMV in New Zealand were identified by the search strategy, and are discussed below in order to provide some real-world context for safety concerns.(47),(48),(49),(50) All were conducted by the New Zealand Ministry of Health with funding from the vaccine manufacturer (Chiron, now Novartis) and careful prospective review of adverse events by an Independent Safety Monitoring Board appointed by the Health Research Council. Adverse events studied included simple febrile seizures (SFS), bronchiolitis, Henoch-Schönlein purpura (HSP) and others.

Increased rates of simple febrile seizures were not observed in post-marketing surveillance of NZ-OMV vaccine. Through active, hospital-based surveillance in the South Auckland area (low socioeconomic status, high proportion indigenous persons) combined with data from the national immunization registry, no increase in febrile seizures were seen at 1, 2, 4 or 7 days post vaccination in children aged 6 months to 4 years between July 2004 and November 2005. The authors estimated that about 63,000 doses were delivered in the region during the study period. The relative risk of SFS within the first 7 days of any dose of NZ-OMV vaccine was 0.68 (95% CI: 0.37, 1.23).(48) Another study reported the rates of pediatric seizures at three hospitals between 2004 and 2006. A total of 17 children under 5 years of age had seizures within four days of vaccinations. Eleven were SFS but nine of these children were diagnosed with a concurrent infection. The authors set two *a priori* acceptable post-vaccination seizure thresholds of 1/10 000 doses and 1/20 000 doses, based on a range of published rates of post-vaccination febrile seizures for routine immunizations. Literature cited included both whole cell and acellular pertussis vaccines. The rate of SFS was 1/28 000 doses and the rate of any seizures post vaccination was 1/18 600 although the authors state that all of the seizures that were not classified as SFS were attributed to other causes. Because the rate of seizures was statistically significantly less than the 1/20 000 threshold, the authors concluded that NZ-OMV vaccine did not increase the risk of simple febrile seizures.(47)

During a phase II study of NZ-OMV vaccine by *Wong et al* (2009)(51) (described in Appendix 2), more bronchiolitis hospitalizations occurred in infants who had received the vaccine versus those who had not (n=5 for those vaccinated with NZ-OMV vaccine plus routine infant vaccines, n=1 for those vaccinated with routine infant vaccines only). As such, the risk of bronchiolitis hospital admission was studied during post-licensure surveillance of NZ-OMV vaccine. Rates of bronchiolitis were assessed using nationwide hospital administrative data and vaccination information was taken from a national immunization registry. Descriptive comparison (seasonal distribution of bronchiolitis in pre- and post- vaccine eras), cohort analysis (using person days at risk) and case-control methodology were used to assess the risk of bronchiolitis hospitalization. Descriptively, the 2005 winter peak of bronchiolitis was temporally-associated with increasing rates of NZ-OMV vaccine vaccination in the population; however, the relative risk of bronchiolitis hospitalization within 60 days of any dose of vaccine was 0.36 (95% CI: 0.33-0.38), which may represent a healthy-vaccine effect. The odds of vaccination in the last 30 days in those with bronchiolitis versus the odds of vaccination in last 30 days in those hospitalized with other illnesses was not significant (odds ratio, OR=0.65; 95% CI: 0.34, 1.24). NZ-OMV vaccine did not increase the risk of bronchiolitis hospitalization in post-licensure surveillance.(49)

A single case of HSP occurred four days post vaccination, early in the vaccination campaign. After this case, HSP was added to the list of conditions to be assessed in hospital surveillance in conjunction with the independent safety monitoring board. In hospital-based surveillance of two hospitals serving the greater Auckland area during a 16-month period, there was no increased risk of HSP in the first seven days after vaccination (RR=0.66; 95% CI: 0.26, 1.72). Additionally, among eight unimmunized children who had had HSP and were subsequently immunized, seven did not develop recurrence.(50)

Other conditions observed in national post-marketing safety surveillance included anaphylaxis, urticaria, anxiety-related events, acute flaccid paralysis (AFP), encephalopathy, thrombocytopenia, hypotonic-hyporesponsive episodes, and Kawasaki disease. All were rare and the authors did not consistently compare rates of these events in vaccinees to baseline rates. There were 64 events of anaphylaxis during the surveillance period of which one was vaccine-related. Two of 11 cases of AFP were found to have 'no cause' and were in children who had received the vaccine. This was not greater than the number of AFP events that would have been predicted to occur if no OMV immunization program had been in place.(47)

III.2.9. CRITICAL APPRAISAL OF NZ-OMV VACCINE STUDIES

Grading of evidence for the efficacy of NZ-OMV vaccine from four cohort studies is presented in Table 6. All studies were graded as level-II-2 and ratings of internal validity ranged from "good" to "poor".

III.2.10. DISCUSSION OF LITERATURE REVIEW

Immunogenicity of 4CMenB vaccine was measured and reported in twelve trials in approximately 5800 healthy participants, of whom 4000 were children aged 2 to 24 months, 84 were children aged 40 to 43 months, and 1738 were adolescents or adults aged 11 to 55 years. These trials assessed the post-vaccination immune response to each vaccine antigen independently, using a combination of hSBA titres (of ≥1:4 or ≥1:5) against selected reference strains H44/76, N5/99 and NZ98/254 and the quantity of antigen-specific IgG, in studies that were conducted prior to the identification of a reference strain (M10713) that primarily expresses NHBA vaccine antigen. Only four trials reported the percentage of participants with hSBA titres against reference strain M10713: two trials, published in *Vesikari et al* (2013)(35), were in infants aged ≤12 months and two trials were in 40 month-old children.(30),(36),(32),(33)

In infants aged ≤12 months, 4CMenB vaccine was found to be immunogenic after at least two or three doses and an anamnestic response to a booster dose, given at 12 months of age, was evident. The infant vaccination schedules assessed include: three doses given at 2, 3 and 4 months of age; three doses given at 2, 4 and 6 months of age with or without a booster at 12 months of age; and three doses given at 6 to 8 months of age, 60 days later and 12 months of age. However, hSBA titres waned prior to the booster dose.(13) Further, 12 months after the booster dose, at age 24 months, hSBA titres were low, especially against strain NZ98/254.(29) Non-inferiority with concomitant vaccines (Infanrix-hexa® and Prevenar®) was also demonstrated; the exception was for the difference in percentage of infants with hSBA titres ≥1:5 when 4CMenB and routine vaccines were given on separate occasions compared to together at 2, 4, 6 months of age, against strain NZ98/254,(22) suggesting that the NZ-OMV component may be impacted by schedule. In a different trial, similar proportions of infants reached the hSBA threshold after a booster dose, with or without concomitant Priorix-Tetra™.(28)

In children aged 12 to 24 months, 4CMenB vaccine was found to be immunogenic against strains H44/76, N5/99 and NZ98/254 after two doses (given at either 12, 14 or 13, 15 months of age),(34) but not after a single dose given at 12 months of age.(13) GMTs were between 32 and 627 one month after the second dose of 4CMenB vaccine, compared to between 1.0 and 1.2 at baseline. However, hSBA titres waned after 9 to 10 months (when measured at age 24 months) and were lowest against strain NZ98/254.(29) A third dose of 4CMenB vaccine given at 24 months of age stimulated hSBA titres of ≥1:5 against strains H44/76, N5/99 and NZ98/254 in all participants.

For the 84 children who received 2 doses of 4CMenB vaccine at 40 and 42 months of life, seroprotection was achieved one month after the second dose for all reference strains by 70–100% of participants, depending on reference strain. The proportion with seroprotective titres was lowest against strain M10713.(32),(33),(30),(36)

In adolescents and adults, 4CMenB vaccine was found to be immunogenic against strains H44/76, N5/99 and NZ98/254 after at least one dose, although higher GMTs were seen after two doses compared to one dose of the vaccine. Responses to a booster dose were also evident in the adolescent trial; at 6 months, at least 91% of adolescents had hSBA titres of ≥1:4 for each of the three reference strains after two or three doses, compared to 73–76% after one dose.(21) In adults, four months after the second dose, 96% and 100% had hSBA titres of ≥1:4 against strains H44/76 and N5/99, respectively, compared to 67% against strain NZ98/254.(38)

Overall, compared to the other selected reference strains, immune responses were generally lowest to strain NZ98/254, the only strain for which there is effectiveness data. This is an interesting finding, given that the NZ98/254 strain expresses identical PorA (P1.4) and NHBA (peptide 2) to 4CMenB vaccine. It also expresses the same fHbp variant 1 (although different sub-variant) as the vaccine, with good cross-reactivity among sub-variants of fHbp variant 1 reported in pre-clinical studies.(10) It has been suggested that the low response of vaccinated sera with this strain may be attributable in part to the level of expression of these antigens by NZ98/254.(13)

Findings from phase II trials comparing the immunogenicity of 4CMenB vaccine to that of a candidate recombinant meningococcal B (rMenB) vaccine without the OMV component, suggest an adjuvant effect of the OMV component.(13),(25) However, these trials did not directly compare the immunogenicity of 4CMenB vaccine to NZ-OMV vaccine. Studies of the immunogenicity of NZ-OMV vaccine among infants and children in New Zealand showed a beneficial effect of a third dose (20). However, similar to 4CMenB vaccine, a fairly rapid decline of bactericidal antibodies was seen after three doses.(52) A fourth dose of NZ-OMV given at 10 months of age (4 months after the primary three dose schedule) elicited a booster response, increasing the percentage of infants achieving the hSBA threshold from 48% after dose three to 69% after dose four (52). Post-licensure NZ-OMV studies estimated the vaccine effectiveness to be between 53.3% and 84% over 2-3 years of observation.

Across eleven of the twelve 4CMenB vaccine trials included in this review, safety was measured and reported in approximately 8200 participants, of whom 6400 were children aged 2 to 24 months, 84 were children 40 to 43 months of age, and 1738 were adolescents or adults aged 11 to 55 years. In these trials, solicited local and systemic reactions were recorded during a seven-day period following vaccination and serious and other adverse events were reported up to six months after the last dose of 4CMenB vaccine.

Among infants and children, common solicited local and systemic adverse events following vaccination with 4CMenB vaccine included erythema, induration and irritability. Among infants, similar proportions of local reactions at the 4CMenB injection site were observed when 4CMenB vaccine and routine infant vaccines were given on separate occasions versus together, except for pain which was higher following concomitant administration.(22) Higher proportions of infants with solicited systemic reactions, including fever, were observed when 4CMenB vaccine was given together with Infanrix-hexa® and Prevenar®(22) or Priorix-Tetra™.(28) Fever was reported in up to 60% of infants and was more common after the first or second dose of 4CMenB vaccine. In the only infant study that used Pediacel® as the DTaP-IPV-Hib vaccine, the proportion that experienced fever was comparatively lower (9.2% all doses, 18% after the first dose) but this study only included 46 4CMenB vaccine recipients and is too small to draw any conclusions regarding the impact of differences in formulation of routine infant vaccines on fever after simultaneous administration of 4CMenB vaccine.

Among children 12 to 24 months old, higher percentages of erythema and induration were observed after the first dose of 4CMenB vaccine, when given together with Priorix-Tetra™ compared to when 4CMenB vaccine is given alone. Rates of solicited systemic reactions after the first dose were also higher among children that received 4CMenB vaccine with Priorix-Tetra™ with the exception of vomiting which was slightly higher among children that received 4CMenB vaccine alone. In terms of fever, 35% and 36% of children experienced fever 1-4 days after the first and second doses of 4CMenB vaccine given at 13 and 15 months of age, respectively.(34) These percentages were slightly lower compared to children who received their first dose of 4CMenB vaccine with Priorix-Tetra™ at 12 months of age and second dose of 4CMenB at 14 months of age (37% and 40% with fever after dose 1 and dose 2, respectively).

Interestingly, although 4CMenB vaccine was given to only 84 children, not previously immunized with 4CMenB vaccine, who were 40 and 42 months old, there was one episode of febrile seizure that occurred 6 hours after immunization and 10 participants experienced severe transient arthralgia. As well, local reactions were very common in this group.(32),(30),(41)

Among adolescents, proportions of local reactions after 4CMenB vaccine were similar with each dose, though the proportions who reported local reactions after the second and third dose were slightly lower than after the first dose. Solicited local reactions were reported from 39% (swelling) up to 86% (pain) of 4CMenB vaccine injections, while systemic reactions were reported from after 4% (fever ≥38°C) up to 51% (malaise) of 4CMenB vaccine doses (all doses combined).(21) Fever was significantly higher following 4CMenB vaccine compared to an alum-containing control (after 4% vs. 2% of 4CMenB vaccine injections, $p<0.0001$), as was the proportion of 4CMenB vaccine recipients that reported using antipyretic drugs (4% vs. 2%, $p<0.0002$). In the single adult study, solicited local reactions were reported by 47% (erythema) up to 98% (pain) of 4CMenB vaccinees, while solicited systemic reactions were reported by 2.6% (fever) up to 38.1% (malaise) (all doses combined). Twelve percent of adolescents and 9% of adults reported staying home as a result of 4CMenB vaccination.

Risk for fever and febrile seizure

According to the authors, no increase of febrile seizures was seen in the initial reports from trials of 4CMenB vaccine. Based on *Vesikari et al* (2013)(35), 4 seizures (all of which were accompanied by fever but two of which were reported as febrile seizures) occurred among 2478 infants <12 months old within 24 hours of receipt of 4CMenB vaccine and routine vaccines. From *Philip et al* (2012)(32), *Saroey et al* (2012)(30), and *Martin et al* (2012)(41), one of 84 children given a primary series of 4CMenB vaccine at 40 and 42 months old had a febrile seizure six hours after 4CMenB vaccine. Because 4CMenB vaccine is not yet approved for use in any jurisdiction, there are no post-licensure, phase IV studies of its safety to establish the true population risk of febrile seizures associated with it. Because there may be significant risk of febrile seizures due to 4CMenB vaccine, just as there is with MMRV vaccine, some points regarding fever and febrile seizure are made below.

Of note, in the single study that used Pediacel® as the pentavalent routine infant vaccine, the risk of fever was lower than in other studies which used Infanrix-hexa™, as discussed above. This could have programmatic implications but more data is needed.

Regarding 4CMenB vaccination of toddlers, in *Prymula, Vesikari, Esposito et al* (2011),(34) a higher proportion of children had fever with temperatures of ≥38°C after the first dose when given 4CMenB vaccine with Priorix-Tetra™ than without (43% vs. 35%, respectively). Although *Prymula, Vesikari, Esposito et al* (2011) reported higher rates of fevers when 4CMenB vaccine was given with Priorix-Tetra™, the rates were lower compared to those reported in other studies assessing fever after the first dose of Priorix-Tetra™ given to participants in the same age.(53) Priorix-Tetra™ is associated with a higher probability of fever with 60% to 68% of participant experiencing fever, and 10% with a fever of ≥39.5°C after the first dose. In the 4CMenB vaccine study by *Prymula, Vesikari, Esposito et al* (2011),(34) 53% of participants reported fever (≥38°C) 5 to 28 days after concurrent administration of 4CMenB vaccine with Priorix-Tetra™. It is important to note that 4CMenB fever peaks at 6 hours after immunization and few fevers persist beyond 2 days after immunization. On the other hand, MMRV fever tends to occur 7-10 days after immunization. Thus, when the vaccines are given simultaneously, there are two risk periods for febrile seizure.

Risk of febrile seizure after the MMRV vaccine ProQuad® (Merck) was lower in trials than observed through post-licensure surveillance and the same situation could occur with 4CMenB vaccine. In MMRV pre-licensure studies conducted among healthy children aged 12-23 months, fever ($\geq$38.9°C) was observed in 21.5% of children who received MMRV (n=4497) compared to 14.9% of children who received MMR vaccine and varicella vaccine concomitantly (n=2038) (risk difference: 6.6% [95% CI: 4.6, 8.5]).(54) Two MMRV post-licensure cohort studies conducted in the United States assessed the risk of febrile seizure among children, aged 12-23 months and were sponsored by Merck(55) or Centers for Disease Control (CDC).(56) Rates of febrile seizures among children who received first dose of MMRV vaccine compared to children who received separate first doses of MMR and varicella vaccines administered at same visit, were: 7.0 per 10 000 vaccinations vs. 3.2 per 10 000 vaccinations for 5-10 day post-vaccination period (RR=2.2; 95% CI: 1.0, 4.7; $p<0.05$) (55),(56); and, 8.5 per 10 000 vaccinations vs. 4.2 per 10 000 vaccinations, unadjusted rates, for 7-10 day post-vaccination period (adjusted RR=2.0; 95% CI: 1.4, 2.9; $p=0.0001$).(56)

This approximately two-fold increased risk translated into one additional febrile seizure per 2300-2600 children vaccinated with first dose of MMRV compared with those who receive first dose as MMR vaccine and varicella vaccine.(54) Post-licensure safety surveillance will be required to determine the population risk of febrile seizures after 4CMenB vaccine.

Aluminum containing placebo

In the only placebo-controlled trial of 4CMenB vaccine, by *Santolaya et al* (2012)(21), there was comparable reactogenicity between 4CMenB vaccine and an aluminum hydroxide control. Rather than an inert, non-reactive placebo, the authors used a potentially reactive placebo containing aluminium, an adjuvant, as their control. Both the control and 4CMenB vaccine contained 1.5 mg of aluminium hydroxide. Since investigators only need to show a non-significant difference in reactogenicity between the study vaccine and a placebo to prove a vaccine is safe, a reactive placebo can inflate the adverse events profile of the placebo, thus artificially increase the safety profile of the study vaccine. Therefore, the reactogenicity and tolerability data for 4CMeB vaccine from the *Santolaya et al* (2012) trial must be interpreted with caution.

Implications of acetaminophen

Prymula et al (2011)$^{(26)}$ assessed the impact of prophylactic paracetamol on the immunogenicity and safety of routine vaccines (Infanrix™-hexa and Prevenar®) when given concomitantly with 4CMenB vaccine at 2, 3 and 4 months of age. There were no significant differences in the immunogenicity of 4CMenB vaccine against reference strains H44/76-SL, N5/99 and NZ98/254 when co-administered with routine vaccines with or without prophylactic paracetamol. It is not clear whether parental administration of paracetamol, independent of the study, was included in usual care in the non-paracetamol group, or if this group was instructed not to take paracetamol. Prophylactic paracetamol was found to reduce febrile events after vaccinations. The proportion of infants with temperature ≥38.5°C was nearly 50% lower in infants who received paracetamol than without (51% vs. 25%). Although temperature ≥39.5°C was uncommon in both groups, a smaller proportion of infants had fever (≥39.5°C) when given paracetamol (1% vs. 5%). Additionally, in both groups, the proportion of infants with fever (≥38.5°C and ≥39.5°C) decreased with each successive dose of 4CMenB vaccine.

Interestingly, when parents of the open-label subset were informed of potential fever events after vaccination in an on-going phase III study (data on file with Novartis), the probability of medically attended fever among infants who received 4CMenB vaccine concomitantly with routine vaccines (Infanrix™-hexa and Prevenar®) was lower in the open-label subset than the observer-blind subset (1.42% vs. 5.27%). Details on whether parents were counseled to prophylactically administer anti-pyretic is unclear as the trial is ongoing and is pending publication.

Based on the study of routine use of acetaminophen with 4CMenB vaccine, it appears that this anti-pyretic does not dampen the immunogenicity of the vaccine. As expected, there were fewer fevers among those who received prophylactic paracetemol. Parental counseling may reduce rates of medically-attended fever.

The results of *Prymula et al* (2011)(26) imply that routine prophylactic administration of acetaminophen an appropriate strategy to counter high rates of fever among infants vaccinated with 4CMenB vaccine. A practice such as this would stray far from current practice. Although there are no recommendations in the Canadian Immunization Guide regarding prophylactic use of anti-pyretics at the time of immunization, parental administration of anti-pyretic drugs, such as acetaminophen/paracetamol or ibuprofen, is generally recommended by health care providers for treatment of the self-limited fever that occurs after vaccination. There is not a typical practice among health care providers regarding prophylactic administration of anti-pyretics to *prevent* vaccine-related fever; some may recommend to do so and others may not. As well, there are no safety data on a practice whereby anti-pyretics are routinely given accompanying each dose of a given vaccine, as the Prymula study seems to suggest. At a population level, there may be adverse hepatoxic adverse events in susceptible infants (those with underlying medical conditions or acute illness, for example).

In addition, concerns have been raised that anti-pyretic drugs could potentially interfere with immunogenicity of routine vaccines(57) after *Prymula et al* (2009)(58) reported significant reductions in antibody responses to several routine vaccine antigens when prophylactic paracetamol was given to infants before and after routine vaccination with ten-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine, Infanrix™-hexa and Rotarix®. In contrast, *Prymula et al* (2011)(26) has since reported no impact of routine paracetamol on the immunogenicity of 4CMenB vaccine, Infanrix-hexa® and Prevenar®.

The complex immunologic interaction between vaccines and anti-pyretics remains not wholly understood. Moreover, while Prymula's work suggests that fever following immunization may be decreased with routine prophylactic doses of acetaminophen, it is not known if prophylactic acetaminophen will reduce the risk of febrile seizure. As well, the population-level impact of a practice such as this must be taken into consideration.

IV. EVIDENCE GAPS

Evidence gaps remain for all of the domains presented in this report and are outlined below. Box 1 highlights recommended strategies to address these needs and the text describes the evidence gaps in detail. These strategies are taken from expertise provided by the NACI meningococcal working group and from the literature. For example, Snape and co-authors(59) recently identified a number of post-implementation surveillance challenges and a number of these are listed in Box 1. Of note, "surveillance" and "research" are intertwined and a recommendation suggested in one area could also be addressed through work in the other.

Box 1: Surveillance and research recommendations to address evidence gaps regarding 4CMenB vaccine

Domain	Specific Concern	Recommendation
Surveillance	Meningococcal epidemiology	Enhanced meningococcal surveillance both prior to and after vaccine implementation. Impact of vaccine on serogroup B and non-serogroup B strains among vaccine program eligible (direct effects) and ineligible (indirect/herd effects) persons.
	Microbiologic characteristics	Laboratories must have capacity to examine traditional microbiologic characteristics of meningococci as well as determine NHBA, NadA, and fHBP types of all isolates. Important role of reference laboratories.

Surveillance	Adverse events following immunization (AEFI)	Enhanced AEFI surveillance such as that of New Zealand "Intensive Vaccines Monitoring Program" for NZ-OMV. Ensure baseline data regarding anticipated adverse events (e.g. febrile seizure) is collected
	Vaccine uptake	Universal immunization registries in all Canadian provinces.
Research	Direct vaccine effectiveness (VE)	Research examining microbiologic characteristics of serogroup B IMD in vaccinated and unvaccinated individuals; examination of vaccine failures. Sero-epidemiologic studies of vaccinated and unvaccinated individuals Calculation of VE using "screening method" if immunization registry present.
	Potential Indirect/herd effects	Studies of nasopharyngeal carriage of meningococci prior to and after vaccine implementation.
	Duration of protection	Sero-epidemiologic studies of immunized persons to look for waning immunity.
	Molecular biology of the meningococcus	Microbiology research describing changes in serogroup, clonal complexes, surface-protein characteristics before and after vaccine implementation.
	Acceptability of vaccine to the general public	Research exploring risk tolerance/ acceptability of the adverse event profile of 4CMenB vaccine.

Evidence gaps can be classified based on research and surveillance needs, as they are above. Alternatively, they are presented below, classified based on a number of the domains NACI must address in order to make a vaccine decision. These include potential to protect against Canadian meningococcal strains, vaccine safety, vaccine efficacy, duration of protection, herd immunity, special populations and surveillance needs. Discussion of these is as follows:

Protection against Canadian meningococcal strains

The immunogenicity data uses hSBA, the accepted correlate of protection against meningococcus, but, for the most part, only measured using four strains of serogroup B *N. meningitides*. Three of the strains express high quantities of one of the surface-exposed proteins included in the vaccine and the fourth contains the PorA OMV of the New Zealand outbreak strain from the 1990s and early 2000s. Little is known about the ability of 4CMenB vaccine to protect against other serogroup B and non-serogroup B meningococcal strains.

Five trials reported the immunogenicity of 4CMenB vaccine against non-reference meningococcal B strains as well as against non-B serogroups. These were: the *Findlow et al* (2010)(13) trial of 4CMenB vaccine versus rMenB vaccine at 2, 4, 6, and 12 months as well as its extension trial (40 month booster), presented by *Saroey et al* (2012)(30) and *Snape et al* (2012)(36); the *Snape et al* (2010)(25) trial of 4CMenB vaccine versus rMenB vaccine at 6, 8, and 12 months and its extension trial (40 month booster), presented by *Philip et al* (2012)(32) and *Snape et al* (2012)(33); and the *Findlow et al* (2012)(39) trial of 4CMenB vaccine in laboratory workers. The paediatric studies assessed immunogenicity in a handful of other serogroup B strains and it was found to be variable (data not extracted for this literature review). In the adult study, *Findlow et al* (2012) examined the immunogenicity of 4CMenB vaccine, given concomitantly with Menveo® against a total of seven serogroup B strains as well as serogroup A [strain F8238, P1.20,9, sequence type (ST)-5, clonal complex (CC)-5]; serogroup C (strain C11, P1.7-1,1, ST-345, CC-unassigned); serogroup W135 (strain M01 240070, P1.18,3, ST-184, CC-22); and serogroup Y (strain M03 2411125, P1.5,2, ST-11, CC-11). The 38 subjects in this study had high baseline seroprotection to the three serogroup B strains that were not reference strains for the vaccine proteins (61-87%) as well as against the serogroup A, C, W135 and Y strains (61–84%). One month after the third dose of 4CMenB seroprotection was 90–100% for the non-reference serogroup B strains and 93–100% for the serogroup A, C, W135 and Y strains. Serogroup A, C, W135 and Y protection is attributed to Menveo®, rather than 4CMenB vaccine. This limited data from two studies of infants and children and one adult study suggests that 4CMenB vaccine protects against some serogroup B strains beyond those used as the reference strains for the vaccine protein.

Beyond direct assessment of immunogenicity, the MATS assay can be used to predict the cross-reactivity of the immunologic response to various meningococcal strains. The authors of MATS literature believe that MATS offers a conservative prediction of the serogroup B meningococcal protection offered by 4CMenB vaccine. MATS of Canadian sample predicted that only 49% (95% CI: 29%, 71%) of serogroup B meningococcal isolates from infants less than 1 year of age could be protected with 4CMenB vaccine.(60) Even if this is an underestimation, a relatively low proportion of estimated response is a concern, especially given that infants have the highest rate of serogroup B IMD in Canada.

There are other considerations related to MATS. The positive bactericidal threshold (relative potency on MATS of each vaccine component above which 80% were ‘killed’ by hSBA) for NHBA was a relative potency of 29.4%, whereas the relative potencies that met positive bactericidal threshold for fHBP and NadA were much lower (2.1% and 0.9%, respectively).(19) Relative potency is essentially a rating of how much of the given protein is expressed (the more expression, the higher the relative potencies). That low relative potencies met positive bactericidal threshold implies organisms with low expression of fHBP or NadA will express enough for the immune response, due to previous immunization, to kill the organisms and prevent disease. However, the very low relative potencies for these two proteins also raise concerns regarding the reproducibility of the assay. As such, MATS results may not translate into *in vivo* protection against serogroup B meningococci. The correlation of MATS and hSBA, which is the crux of the MATS assay, was based on very few data points (i.e., 5, 11 and 7 strains were selected for fHbp, NHBA and NadA, respectively) and the Donnelly paper is the only paper to assess the correlation between MATS and hSBA. Using pooled sera from 13-month-olds who had received 4CMenB (3+1) schedule, 89% of tested strains that were above the positive bacterial threshold for one or more antigens were “killed” by the hSBAS. Seventy-seven percent of tested strains that were below the positive bacterial threshold were also "not killed" by hSBA. This means that 11% were falsely positive on MATS and 23% were falsely negative. The proportion of false positives and false negatives must be considered when interpreting MATS data.

Given the lack of understanding of how immunogenicity against four specific meningococcal strains will translate into either efficacy or effectiveness against circulating meningococcal strains, there is a need to define how well the various tests (hSBA, MATS) correlate with protection, both on the individual level (hSBA) and at a broader, population level. A case-control study comparing hSBA results against specific Canadian strains among infected and uninfected persons, and examining immunization status, could be valuable. There may also be a role for other sero-epidemiologic studies.

Safety

From a safety point of view, NZ OMV was safe when a national program was instituted in New Zealand, a small (population 4.4 million, 2012), geographically isolated country that was experiencing an outbreak of a hypervirulent meningococcal serogroup B clone. There was no increased risk of febrile seizures during a two year period, in this small country. However, rates of fever were very low in NZ-OMV trials (10–20%, see Appendix 2). Given the very high rates of fever with 4CMenB vaccine in trials, the much larger Canadian population, and the longer intended timeline for use, it is possible that an association between 4CMenB vaccine and febrile seizure will be observed in Canada. The evidence of post-vaccination febrile seizure when MMRV was used population-wide in the United States, even though this had not be observed in clinical trials indicates the need for enhanced surveillance of adverse events following immunization (AEFI) in conjunction with the 4CMenB vaccination programs. Of note, febrile seizures in infants less than 6 months old, which is outside the typical age range for simple febrile seizures, will need to be monitored closely as these types of seizures require more extensive hospital-based management and investigations.

Efficacy

It is not unusual for evidence to be lacking regarding efficacy and effectiveness of a vaccine against a rare infectious disease such as serogroup B IMD before approval for use. Unique from other rare vaccine preventable diseases, there is experience with a single component of 4CMenB vaccine, the P1.7-2,4 OMV. This vaccine has an estimated efficacy of around 70% in the context of a waning outbreak; however, the generalizability of the NZ OMV efficacy to predicted efficacy of 4CMenB vaccine is unknown. Across Canada there is geographic variability in the proportion of serogroup B meningococcal isolates that express PorA P1.4. In Atlantic Canada, especially in New Brunswick, meningococcal B strains with P1.4 are common (e.g. 71.4% [15/21] of serogroup B isolates in New Brunswick contained P1.4, between 2005 and 2010). On the other hand, in Québec, only 1.8% (6/334) of serogroup B isolates expressed P1.4 between 2003-2010 (National Microbiology Laboratory and Laboratorie de Santé Publique du Québec, unpublished data) and in Ontario, during 2001-2010, 28 of 193 (14.5%) serogroup B meningococcal isolates expressed PorA P1.4 and 2 expressed P1.4 variants.(61) Based on data from the current national enhanced meningococcal surveillance program, between 2005 and 2010, 9.6% of all serogroup B isolates expressed P1.4 and 5.3% of all isolates (any serogroup) expressed P1.4 (National Enhanced Invasive Meningococcal Disease Surveillance System: National Microbiology Laboratory and Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada). Further enhanced meningococcal surveillance with concerted efforts to obtain detailed vaccination status among cases and microbiologic information will be important, including PorA genotype and sequence type, as well as determining the presence of the vaccine surface exposed proteins included in 4CMenB vaccine. Post-licensure surveillance will be important to accurately evaluate vaccine effectiveness, potential vaccine-escape mutant, and safety.

Duration of protection

Studies to date have only measured immunogenicity of 4CMenB vaccine 12 months after the completion of 3+1 infant schedule; 6 months after the completion of two doses in adolescence; and 1 month after two doses in adulthood. There is no data regarding levels of circulating antibodies beyond these short periods and, as such, the duration of protection of 4CMenB vaccine is unknown.

Herd Immunity

Because 4CMenB vaccine has not yet been used at a population level, it is not known if it will confer herd immunity. There are ongoing studies, not included in this literature review report, examining the effect of 4CMenB vaccine on nasopharyngeal carriage of meningococci and this may shed some light on its potential for herd effects. Other vaccines, that eliminate nasopharyngeal carriage, including serogroup C meningococcal conjugate vaccine, have conferred herd immunity. For example, in a comparison of one year (July 1998-June 1999) prior to the introduction of serogroup C meningococcal conjugate vaccine to the routine childhood immunization schedule in the UK to a one year (July 2001-June 2002) period after the program began, a 35% (95% CI: 20%, 49%) decrease in the incidence of serogroup C IMD was observed among adults greater than 25 years old. In this vaccine ineligible group, the rate of serogroup C IMD went from 0.53/100 000 to 0.34/ 100 000.(62) It is possible that a similar herd immunity phenomenon may be seen with 4CMenB vaccine but this remains unknown.

Special populations

As stated in the Contraindications and Precautions section above, there are no studies that assess the safety and immunogenicity of 4CMenB in pregnant women, persons with chronic medical conditions, and those with a history of serogroup B IMD. Evidence regarding the safety and immunogenicity in high-risk groups, such as those with complement deficiencies is also unavailable.

Surveillance needs

A number of recommendations regarding research and surveillance were discussed above. A robust surveillance system for serogroup B IMD and AEFI are necessities to assess the impacts, both positive and negative, of 4CMenB vaccine. The surveillance systems that currently exist in many Canadian provinces may not be adequate.

V. SUMMARY

This document serves as a literature review report regarding the safety and immunogenicity of 4CMenB vaccine, and the safety, immunogenicity and effectiveness of its precursor vaccine, NZ-OMV; it also serves as a source of information regarding unique technical considerations related to 4CMenB vaccine and other vaccine characteristics. See section III.2.10 for detailed discussion and critical appraisal of the literature review section.

In summary, 4CMenB vaccine is a novel vaccine designed to target meningococcal surface-exposed proteins (NHBA, NadA, fHPB and OMV prepared from strain NZ98/254). It has been proven immunogenic though the duration of follow-up in studies to date has been short and this is notable because, as described by Harrison, it appears that high circulating anti-meningococcal antibodies are required to prevent disease after exposure.(63)

Regarding safety, the rate of fever after immunization is very high, though reduced if either anti-pyretics are administered or if 4CMenB vaccine is given at a separate visit from routine vaccines. Both of these potential strategies to reduce fever following immunization have implications that must be considered. While, based on a single study, simultaneous anti-pyretics do not appear to blunt the immune response to 4CMenB vaccine, there is no data regarding the safety of routine prophylactic administration of anti-pyretics at the time of immunization to all vaccinees. The delivery of 4CMenB vaccine on separate occasions from other childhood immunizations would inconvenience families, reduce the feasibility of a 4CMenB vaccine program, increases the cost of providing vaccinations and possibly lead to missed vaccinations.

The most serious anticipated AEFI with 4CMenB vaccine is febrile seizure. In trials, there were very few febrile seizures but sample sizes are small. Given the recent concern with MMRV and rates of febrile seizures when it was used at a population level, there may be a real risk of unacceptably high rates of febrile seizures with 4CMenB vaccine. Another potential serious adverse event, observed in trials, is juvenile arthritis. The true risk of these serious adverse events is not yet known.

MATS was designed to predict how well 4CMenB vaccine will protect against circulating meningococcal strains. Canadian data to date predicts that 4CMenB vaccine will protect against somewhere between 40% and 80% of serogroup B meningococcal infections, depending on age group. Of note, in Ontario, Canada's largest province, the rate of serogroup B is highest in infants less than one year of age but it is predicted that only 40% of strains affecting this age group will be covered by the 4CMenB vaccine based on MATS results.

The evidence gaps discussed in section IV must be noted. There is currently no data regarding the use of 4CMenB vaccine in some age groups and special populations (e.g., those at increased risk of IMD due to complement deficiency or asplenia).

As noted above, the 'predicted' ability for 4CMenB vaccine to prevent Canadian IMD remains only a prediction through the MATS assay. These evidence gaps are opportunities for further study. Enhanced meningococcal surveillance; post-licensure surveillance for adverse events following immunization (AEFIs), especially febrile seizures; and sero-surveillance projects (e.g., comparison of sera of those with serogroup B IMD and unaffected persons regarding presence of anti-fHBP, anti-NadA, anti-NHBA and anti-OMV, would all be of great value.

VI. CONCLUSIONS

The current report addresses the safety and immunogenicity of 4CMenB vaccine and the safety, immunogenicity and effectiveness of the NZ-OMV vaccine, since NZ-OMV is found in the 4CMenB vaccine. Concerns regarding short duration of follow-up, high rates of fevers, and small sample sizes in phase II and phase III clinical trials have been presented. This document also provides technical information regarding the unique production of this vaccine and prediction of strain coverage as well as general vaccine information such as storage and schedule. Evidence gaps and NACI recommendations for research and surveillance have also been described.

At present, 4CMenB vaccine is an immunogenic vaccine, though duration of protection is unknown and, rates of vaccine-related fever were high in trials though there was no increased risk of febrile seizures among infants vaccinated in trials. Should 4CMenB vaccine be used at a population level, with a much larger denominator than a clinical trial, there may be unacceptably high occurrences of febrile seizure following immunization. As well, Canada's infants are most vulnerable to serogroup B IMD but predicted protection against strains that infect Canadian infants is low.

Further research is required to determine the duration of protection, the efficacy or effectiveness of 4CMenB vaccine, and the risk of febrile seizure with wide-spread use. As well, enhanced meningococcal surveillance including detailed laboratory characterization of organisms and special serological studies of cases are necessary. Given all the uncertainty around 4CMenB vaccine, it is recommended that the vaccine not be used unless a comprehensive plan is implemented to evaluate its impact through surveillance and research, as a pre-requisite to implementation.

This literature review report was used to inform the evidence-based NACI Statement (http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php) regarding 4CMenB vaccine.

VII. LIST OF ABBREVIATIONS

Abbreviation	***Term***
4CMenB	Multicomponent meningococcus serogroup B
AEFI	Adverse Events Following Immunisation
AFP	acute flaccid paralysis
Agency	Public Health Agency of Canada
CFR	Case fatality ratio
CIRID	Centre for Immunization and Respiratory Infectious Diseases
CI	confidence interval
CV	chiron vaccines
DPTPHib	diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b and inactivated poliovirus
DTap-HBV-IPV/Hib	diphtheria, tetanus, acellular pertussis, inactivated polio, Haemophilus influenzae type b and hepatitis B
ELiSA	enzyme-linked immunosorbent assay
fHbp	Factor H binding protein
GMC	geometric mean concentration
GMT	Geometric mean titre
GNA	Genome-derived neisserial antigen
hSBA	human complement serum bactericidal activity
IgG	Immunoglobulin G
IM	intramuscular
IMD	Invasive meningococcal disease
IMPACT	Immunization Monitoring Program, ACTive
ITT	Intention-to-treat
KD	Kawasaki Disease

LL	lower limit
MCCV-Hib	meningococcal serogroup C and Hib conjugate vaccine
MenACWY-CRM	meningococcal serogroups A, C, W-135 and Y conjugate vaccine
MMR	measles, mumps, rubella vaccine
MMRV	measles, mumps, rubella and varicella vaccine
N. Meningitidis	*Neisseria Meningitidis*
NACI	National Advisory Committee on Immunization
NHBA	Neisseria heparin-binding antigen
NadA	Neisserial adhesion A
NIPH	Norwegian Institute of Public Health
NZ	New Zealand
nCAM	neural cell adhesion molecule
MATS	Meningococcal Antigen Typing System
MBPPTG	Meningococcal B Pilot Project Task Group
MLST	Multilocus sequence typing
OMP	Outer membrane proteins
OMV	Outer membrane vesicle
PorA	Porin A
PP	per protocol
P/Ts	Provinces and Territories
RCT	Randomized controlled trial
rMenB	Recombinant meningococcal B
SAE	serious adverse event
SD	standard deviation
ST	sequence type
VE	Vaccine Effectiveness

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X. APPENDICES

APPENDIX 1: LITERATURE SEARCH STRATEGY FOR MEDLINE

Database: Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® <1946 to Present> Searched on January 4, 2012; Search Strategy:

1 Neisseria meningitidis/ or neisseria meningitidis.mp. (8751)
2 Neisseria meningitidis, Serogroup B/ (320)
3 meningococcal infection.mp. or Meningococcal Infections/ (5023)
4 Meningitis, Meningococcal/ (4177)
5 meningococcal disease.mp. (2582)
6 meningococcal serogroup B.mp. (59)
7 (meningococc* adj serogroup B).mp. (68)
8 (meningococc* adj group B).mp. (159)
9 or/1-8 (13392)
10 Vaccines/ or Vaccination/ (57750)
11 vaccin*.mp. (232394)
12 Immunization/ (40073)
13 Antigens, Bacterial/ (36255)
14 Recombinant Proteins/ or recombinant protein.mp. (176296)
15 (factor H binding protein or neisserial adhesin A or neisserial heparin-binding antigen).mp. (86)
16 (fHbp or NadA or NHBA).mp. (308)
17 Bacterial Outer Membrane Proteins/ or outer membrane protein.mp. (18159)
18 (outer membrane vesicle or OMV).mp. (391)
19 (Porin A or PorA).mp. (418)
20 (MeNZB or rMenB or 4CMenB or Bexsero).mp. (40)
21 or/10-20 (468123)
22 Meningococcal Vaccines/ (1917)
23 (efficac* or effective*).mp. (1294655)

24 Carrier State/ or Immunity, Herd/ or (carrier or carriage or herd immunity).mp. (177994)
25 immunogenic*.mp. (35503)
26 reactogenic*.mp. (1578)
27 Antibodies, Bacterial/ or antibod*.mp. (878603)
28 Serum Bactericidal Test/ or Blood Bactericidal Activity/ or Serum Bactericidal Antibody Assay/ (5433)
29 bactericidal.mp. (22447)
30 Bacterial Typing Techniques/ (13263)
31 Enzyme-Linked Immunosorbent Assay/ or (enzyme-linked immunosorbent assay or ELISA).mp. (168326)
32 (meningococcal antigen typing system or MATS).mp. (1528)
33 (adverse or side or tolerab* or safe* or complication* or fever* or seizure*).mp. (1824669)
34 contraindications.fs. (15293)
35 adverse effects.fs. (1196807)
36 complications.fs. (1429418)
37 chemically induced.fs. (443512)
38 or/23-37 (5598957)
39 ([9 and 21] or 22) and 38 (3247)
40 limit 39 to (english language and humans) (2239)
41 limit 40 to yr="2005 -Current" (882)

APPENDIX 2: IMMUNOGENICITY AND SAFETY OF NZ-OMV VACCINE

X.1 IMMUNOGENICITY OF NZ-OMV VACCINE

Infants ≤12 months old

The immunogenicity of the NZ-OMV vaccine with or without routine vaccines was assessed in healthy infants in two phase II clinical trials(51),(64) and one persistence study.(65) All three studies were conducted in Auckland, New Zealand. The following vaccination schedules were assessed: 3 doses given at 6 weeks, 3 months and 5 months of age; 4 doses given at 6 weeks, 3 months, 5 months and 10 months of age; and 3 doses in a 6-weeks interval schedule.

In the *Wong et al* (2009)(51) trial, 250 out of 375 healthy 6 to 10 week old infants were randomized to receive three doses of NZ-OMV vaccine administered with routine vaccines (Infanrix-IPV™, GlaxoSmithKline [6 weeks, 3 months, 5 months of age]; Comvax™, Merck [6 weeks and 3 months of age]; or Hb-vax-II™, Merck) at 6 weeks, 3 months, and 5 months of age. A fourth dose was also given at 10 months of age to the first 60 infants that were randomized. In infants vaccinated with 3 doses of NZ-OMV vaccine, 8% (95% CI: 5%, 12%) had hSBA titres ≥1:4 against NZ98/254 (B:15:P1.7,16) at baseline. After the third dose (day 151), 76% (95% CI: 70%, 81%) of infants achieved this titre. Seroconversion, defined as 4-fold or greater increase in hSBA titre compared with pre-vaccination baseline, was achieved by 53% (95% CI: 46%, 59%) of infants after the third dose. GMTs were 9 (95% CI: 7, 10) four weeks after the third dose.

In infants vaccinated with 4 doses of NZ-OMV vaccine, 7% (95% CI: 2%, 17%) had hSBA titres ≥1:4 against NZ98/254 at baseline. The proportion of infants that achieved this titre was 74% (95% CI: 61%, 84%), 27% (95% CI: 17%, 41%), and 82% (95% CI: 68%, 91%) after the third dose (day 151), before the fourth dose (day 256), and after the fourth dose (day 298), respectively. Seroconversion was achieved by 45% (95% CI: 33%, 58%), 14% (95% CI: 7%, 26%) and 69% (95% CI: 54%, 80%) of infants after the same time periods. GMTs were 8 (95% CI: 5, 13), and 22 (95% CI: 12, 39) respectively after the third dose, and 4 to 6 weeks after the fourth dose.

In a trial by *Jackson et al* (2009)(64), 237 out of 296 healthy 6 to 8 months old infants were randomized to receive three doses of NZ-OMV vaccine administered in a 6-week interval vaccination schedule. At baseline, one infant had hSBA titres ≥4 against reference strain NZ98/254 (B:4:P1.7b,4); however, 6 weeks after the second dose, and 4 to 6 weeks after the third dose, 86% and 92% of infants achieved this titre, respectively. Results did not differ between the intention-to-treat (ITT) and per protocol (PP) analyses. Seroconversion, defined as a 4-fold or greater increase in hSBA titre compared with pre-vaccination baseline titre, was achieved by 68% and 74% of infants, 6 weeks after the second dose, and 4 to 6 weeks after the third dose, respectively. Results were not different between the ITT and PP analyses. GMTs were not significantly different between the ITT and PP analyses. GMTs were 11 (95% CI: 10, 13) six weeks after the second dose, and 17 (95% CI: 15, 20) four to six weeks after the third dose in the ITT analysis, compared to 11 (95% CI: 9, 13), and 16 (95% CI: 14, 19) in the same time period after the second and third dose, respectively, for the PP analysis.

In a persistence study by Jackson et al (2011)(65), as part of an extension of *Jackson et al* (2009)(64) described above, the same author assessed the immunogenicity of NZ-OMV vaccine one, and seven months after the third dose in a subset of infants (N=40; from *Wong et al* [2009](51)) that previously received 3 doses of NZ-OMV vaccine in a 6-week interval schedule. In this study, Jackson and colleagues reported 97.4% (95% CI: 85.4%, 100.0%) and 92.3% (95% CI: 78.8%, 98.0%) of infants with hSBA titres ≥1:4 and ≥1:8 against strain NZ98/254 one month after the third dose, respectively. At seven months after the third dose, 27.5% (95% CI: 16.1%, 43.0%) and 12.5% (95% CI: 5.1%, 26.7%) met the antibody threshold, respectively. GMTs were 27 (95% CI: 19, 39) and 2 (95% CI: 2, 3) one and seven months after the third dose, respectively.

Children 12 to 24 months of age

Immunogenicity of NZ-OMV vaccine was assessed in healthy children 12 to 24 months of age in one phase II clinical trial(51) and one booster study.(65) Both studies were conducted in Auckland, New Zealand. The following vaccination schedules were assessed: 3 doses in a 6-weeks interval schedule; and a booster at 17 or 11 months after the third dose.

In the small phase II study, *Wong et al* (2009)$^{(51)}$ assessed the immunogenicity of NZ-OMV vaccine administered in healthy 16 to 24 month old children. A total of 265 out of 332 children in this age group were randomized to receive three doses of NZ-OMV vaccine administered in a 6-week interval schedule. At baseline, 2.2% of children had hSBA titres ≥1:4 against reference strain NZ98/254 (B:4:P1.7b,4). Four to six weeks after the third dose, 92% (95% CI: 88%, 95%) achieved this titre. In the ITT analysis, seroconversion, defined as a 4-fold or greater increase in hSBA titre compared with pre-vaccination baseline titre, was achieved by 62% (95% CI: 56%, 67%), and 75% (95% CI: 69%, 80%) of children 6 weeks after the second dose and 4 to 6 weeks after the third dose, respectively. Seroconversion results were not significantly different in the PP analysis. In the ITT analysis for the same time periods, seroconversion against the Norwegian parent vaccine strain H44/76 (B:15:P1.7,16) was achieved by 4% (95% CI: 2%, 8%), and 5% (95% CI: 3%, 9%), respectively. Results were not significantly different for the PP analysis. In both the ITT and PP analysis, GMTs were 10 (95% CI: 9, 11) and 16 (95% CI: 14, 18), 6 weeks after the second dose, and 4 to 6 weeks after the third dose, respectively.

In a booster study, as part of an extension of the *Wong et al* (2009)$^{(51)}$ trial, *Jackson et al* (2011)$^{(65)}$ assessed the immunogenicity of a booster dose NZ-OMV vaccine given to children 12 to 24 months of age that previously received 3 doses of NZ-OMV vaccine in a 6-week interval schedule. The booster dose was given at 17 months after the third dose in children who met the pre-specified definition for seroconversion after the primary trial (responders), and was given 11 months after the third dose in children who did not met this definition (non-responders). Among the responders, 100.0% (95% CI: 90.4%, 100.0%) had hSBA titres ≥1:4 and ≥ 1:8 against reference strain NZ98/254 one month after the third dose; however 20.0% (95% CI: 10.8%, 34.1%) and 6.7% (95% CI: 1.7%, 18.7%) of children had titres ≥1:4 and ≥1:8 eleven months after the third dose, respectively, compared to 34.1% (95% CI: 21.6%, 49.5%) and 17.1% (95% CI: 8.3%, 31.7%) had these titres before the booster dose (17 months after the third dose), respectively. One month after the booster dose, 100.0% (95% CI: 89.8%, 100.0%) had hSBA titres ≥1:4 and ≥1:8. GMTS were 24 (95% CI: 19, 30), 2 (95% CI: 1, 2), 3 (95% CI: 2, 4), and 259 (95% CI: 184, 363), one, 11, and 17 months after the third dose, and 1 month after the booster dose, respectively.

Among the non-responders, 63.3% (95% CI: 45.4%, 78.1%) had hSBA titres ≥1:4 one month after the third dose, and 3.3% (95% CI: 0.0%, 18.4%) had this titre before the booster dose (11 months after the third dose). No non-responders achieved titres ≥1:8 at these time points. One month after the booster, 100.0% (95% CI: 86.2%, 100.0%) of children achieved titres ≥ 1:4 and ≥1:8. GMTs were 4 (95% CI: 3, 5), 1 (95% CI: 1, 1), and 69 (95% CI: 46, 106), 1 and 11 months after the third dose and one month after the booster, respectively.

Children 2 to 17 years of age

There are no studies assessing the immunogenicity of NZ-OMV vaccine in children aged 2 to 7 years or 13 to 17 years.

In one phase II clinical trial(66) and one persistence study(65) conducted in Auckland, New Zealand, the immunogenicity of NZ-OMV vaccine and the Norwegian Institute of Public Health OMV vaccine (NIPH-NZOMV) administered in healthy school children 8 to 12 years of age in a 6-week interval schedule was assessed.

In the *Hosking et al* (2007)(66) trial, a total of 313 children in this age group were randomized in 4:1 ratio to receive three doses of NZ-OMV vaccine produced by Chiron Vaccines (now Novartis) (n=250) or the Norwegian Institute of Public Health (NIPH) (n=63) in a 6-week interval schedule. At baseline, 11% (95% CI: 7%, 15%) of children in both arms had hSBA titres ≥1:4 against strain NZ98/254 (B:4:P1.7b,4); this proportion did not differ between the ITT and PP analysis. In the ITT analysis, 95% (95% C: 91%, 97%) and 89% (95% CI: 78%, 95%) of children achieved this titre 4 to 6 weeks after the third dose of NZ-OMV vaccine and NIPH-NZOMV, respectively; results were not significantly different in the PP analysis. Seroconversion, defined as a 4-fold or greater increase in hSBA titre compared with pre-vaccination baseline titre, was achieved by 73% (95% CI: 67%, 78%) and 71% (95% CI: 58%, 81%) of children, six weeks after the second dose of NZ-OMV vaccine and NIPH-NZOMV, respectively. At 4 weeks after the third dose of NZ-OMV vaccine and NIPH-NZOMV, the proportion of children that achieved seroconversion was slightly higher, although not significant, at 79% (95% CI: 73%, 84%) and 79% (95% CI: 62%, 85%), respectively; results following the second and third dose of either vaccine did not differ between the ITT and PP analyses. GMTs at 6 weeks after the second dose and 4 weeks after the third dose were 20 (95% CI: 16, 24) and 25 (95% CI: 20, 30) for NZ-OMV vaccine, and 20 (95% CI: 13, 30) and 26 (95% CI: 17, 39) for NIPH-NZOMV, respectively; results were not significantly different between the ITT and PP analyses.

In a persistence study, as part of an extension of the *Hosking et al* (2007) trial, *Jackson et al* (2011)(65) assessed the immunogenicity of NZ-OMV vaccine one and four months after the third dose in a subset of infants (N=91) that previously received 3 doses of NZ-OMV vaccine in a 6-week interval schedule. In this study, 85.6% (95% CI: 76.6%, 91.4%) and 74.4% (95% CI: 64.5%, 82.3%) of children had hSBA titres ≥1:4 and ≥1:8 against strain NZ98/254 one month after the third dose, respectively. Four months after the third dose, 44.4% (95% CI: 34.6%, 54.7%) and 26.7% (95% CI: 18.6%, 36.7%) of children met the antibody thresholds, respectively. GMTs were 18 (95% CI: 13, 25) and 4 (95% CI: 3, 6) one, and four months after the third dose, respectively.

Adults 18 to 50 years of age

Jackson et al (2011)(65) assessed the persistence of immune response to NZ-OMV vaccine at months 1, 10, 16 and 22 after the third dose in a small cohort of healthy adults aged 18 to 50 years that previously received 3 doses of NZ-OMV vaccine that contained either 25 µg (N=20) or 50 µg (N=18) of OMV antigen in a 6-week interval schedule in a phase I/II clinical trial by *Thornton et al* (2006)(67) conducted in Auckland, New Zealand. Among adults that received 3 doses of 25 µg NZ-OMV vaccine, 95.0% (95% CI: 74.3%, 100.0%) and 80.0% (95% CI: 57.7%, 92.3%) of adults had hSBA titres ≥1:4 and ≥1:8 one month after the third dose, respectively. Ten months, 16, and 22 months after the third dose, 50.0% (95% CI: 30.0%, 70.0%), 61.1% (95% CI: 38.5%, 79.6%), and 61.1% (95% CI: 38.5%, 79.6%), had titres ≥1:4, and 40.0% (95% CI: 21.9%, 61.4%), 44.4% (95% CI: 24.6%, 66.3%), and 38.9% (95% CI: 20.4%, 61.5%) had titres ≥1:8, respectively. GMTs were 27 (95% CI: 14, 52), 5 (95% CI: 3, 11), 8 (95% CI: 3, 17), and 7 (95% CI: 3, 15) one, 10, 16 and 22 months after the third dose, respectively.

Among adults that received 3 doses of 50 μg NZ-OMV vaccine, 94.1% (95% CI: 70.7%, 100.0%) of adults had hSBA titres ≥1:4 and ≥1:8 one month after the third dose. Ten, 16 and 22 months after the third dose, 64.7% (95% CI: 41.1%, 82.7%), 73.3% (95% CI: 47.5%, 89.3%), and 66.7% (95% CI: 41.5%, 84.8%) had titres ≥1:4, and 47.1% (95% CI: 26.3%, 69.0%), 60.0% (95% CI: 35.7%, 80.1%), and 53.3% (95% CI: 30.2%, 75.1%) had titres ≥1:8, respectively. GMTs were 25 (95% CI: 15, 43), 6 (95% CI: 3, 11), 10 (95% CI: 4, 23), and 9 (95% CI: 4, 19) one, 10, 16 and 22 months after the third dose, respectively.

Adults > 50 years of age

There are no studies assessing the immunogenicity of NZ-OMV vaccine in adults over 50 years of age.

X.2 SAFETY OF NZ-OMV VACCINE

The findings from four phase II and phase III trials addressing the safety of NZ-OMV vaccine in infants and children are described below.

Infants ≤12 months of age

Wong et al (2009)(51) compared the reactogenicity and tolerability of NZ-OMV vaccine in infants that received three doses of NZ-OMV vaccine co-administered with routine vaccines (Infanrix-IPV™, GlaxoSmithKline [6 weeks, 3 months, 5 months of age]; Comvax™, Merck [6 weeks and 3 months of age]; or Hb-vax-II™, Merck [5 months of age]) at 6 weeks, 3 months, and 5 months of age, with routine vaccines alone (Infanrix™, GlaxosmithKiline [6 weeks, 3 months, 5 months of age]; IPOL™, CSL/Aventis [6 weeks, 3 months, 5 months of age]; Comvax™ [6 weeks, 3 months]; Hb-vax-II™ [5 months of age]) (control group). After each dose, rates of local reactions at the NZ-OMV vaccine site were similar to those observed at each routine vaccine sites. The most common local reaction was tenderness and was more prominent at the NZ-OMV vaccine and Infanrix™ sites, and was more frequently observed among infants that were given NZ-OMV vaccine concomitantly with routine vaccine ($p<0.0001$). At the NZ-OMV vaccine site, tenderness was generally described as minor and often occurred within 6 hours after each dose. Systemic reactions occurred more frequently in the

NZ-OMV vaccine with routine vaccines group than the control ($p \leq 0.05$ for each reaction), with exception of vomiting ($p=0.36$) and development of a rash ($p=0.78$). The most common systemic reaction was irritability which occurred in 95% (95% CI: 92%, 97%) and 89% (95% CI: 82%, 93%) of infants after at least one dose of NZ-OMV vaccine with routine vaccines, and routine vaccines alone, respectively. Rates of fever with temperatures ≥38°C was significantly higher in infants that received NZ-OMV vaccine concomitantly with routine vaccines compared to routine vaccines alone, with probabilities of 44% (95% CI: 38%, 50%) compared to 10% (95% CI: 6%, 17%), respectively. In both groups, fever with temperature ≥39°C was rare. Analgesic use was significantly higher in infants that received NZ-OMV vaccine concomitantly with routine vaccine with a probability of 86% (95% CI: 81%, 90%) compared to 67% (95% CI: 59%, 75%) in infants that received routine vaccines alone.

Wong et al (2009) also assessed the reactogenicity and tolerability of NZ-OMV vaccine in a subset of infants that received a fourth dose (N=60). A significantly higher proportion of infants had erythema and induration at the injection site following the fourth dose than the previous doses. Rates of swelling and tenderness were similar across all doses. Systemic reactions following the fourth dose were comparable to those observed following the previous doses with exception of irritability which was significant lower after the fourth dose. The proportion of infants with fever (≥38°C and ≥39°C) or used analgesics were comparable across all four doses.

During the study, *Wong et al* (2009) reported a total of 20 hospital admissions. The most common reasons for admissions were respiratory illness or elective surgery. Among the 14 acute admissions, 12 were from the NZ-OMV vaccine with routine vaccine group, and included bronchiolitis (n=5), pneumonia (n=2), croup (n=1), obstructive apnea (n=1), infected eczema (n=1), and urinary tract infection (n=1). The other 2 acute admissions were from the control group, and included bronchiolitis (n=1) and failure to thrive (n=1). All hospitalizations were judged to be unrelated to NZ-OMV vaccine and routine vaccines. These non-elective admissions occurred in 4.8% and 1.6% of infants in the NZ-OMV vaccine with routine vaccine, and the control group, respectively ($p=0.12$).

Jackson et al (2009)(64) compared the reactogenicity and tolerability of three doses of NZ-OMV vaccine with Menjugate (Novartis) (*control group*), administered in infants in a 6-week interval schedule. Infants were aged 6-8 months and administration of concomitant vaccines is not noted in the methods. NZ-OMV vaccine was associated with a greater proportion of local reactions at the injection site (erythema, induration, swelling and tenderness) following vaccination than Menjugate ($p<0.001$ for each local reaction), with 61–66% and 37–39% of infants having at least one local reaction following each dose of NZ-OMV vaccine and Menjugate, respectively. The most frequent local reaction described following vaccination were induration and tenderness which occurred in 41–49%, and 35–40% respectively of infants in the NZ-OMV vaccine group, compared to 15–19%, and 17–24% respectively in the control group. Severe tenderness, defined as pain on limb movement, was experienced by 3–4% of infants following each dose of NZ-OMV vaccine. Systemic reactions occurred in 64–72% of infants that received NZ-OMV vaccine compared to 41–58% of infants that received Menjugate. Irritability ($p=0.008$), analgesic use ($p=0.01$) and sleepiness ($p=0.02$) were more common in infants that received NZ OMV, and occurred in 46–52%, 43–50% and 11–27% of infants in the NZ-OMV vaccine group compared to 24–42%, 29–36%, and 8–12% in the control group, respectively. Rates of fever, defined as axillary temperature ≥38°C, were 35/235 (15%) after dose one, 39/233 (17%) after dose two and 33/232 (14%) after dose three of NZ-OMV vaccine, compared to 8/59 (14%) after doses one and three and 5/59 (8%) after dose two of Menjugate. Further, use of analgesics was significantly more common following vaccination with NZ-OMV (43–50% NZ-OMV vs. 29–36% Menjugate; $p=0.01$). Two febrile convulsion events occurred following the second dose of NZ-OMV vaccine, however both were deemed to be associated with concurrent illness.

Children 12 to 24 months of age

Wong et al (2007)(68) compared the reactogenicity and tolerability of three doses of NZ-OMV vaccine with the Norwegian parent OMV (NW-OMV) vaccine (B:15:P1.7,16; H44/76) (*control group*) administered in healthy 16 to 24 month old children in a 6-weeks interval schedule. Rates of local reactions at the injection site in both groups were similar across all doses with exception of severe induration which was significantly greater in the NZ-OMV vaccine group ($p=0.006$). The most common local reaction reported in both group was tenderness, and was reported by 73–76% of children in the NZ-OMV vaccine group and 64–74% in the NW-OMV vaccine group; tenderness experienced by the NZ-OMV vaccine group increased in severity with each successive dose ($p<0.001$). No significant differences in systemic reactions were observed across all doses in the two groups. The most common systemic reaction experienced was irritability and was reported 38–44% of children in the NZ-OMV vaccine group and 31–50% in the NW-OMV vaccine group. The proportion of sleepiness ($p=0.01$) and rash ($p=0.02$) experienced in both groups decreased with each successive dose. Fever with axillary temperatures ≥38°C was experienced by 9–11% and 3–11% of children in the NZ-OMV vaccine and NW-OMV vaccine groups, respectively. There was no difference in the use of analgesics between the two groups. In this trial, no vaccine-related serious adverse events were reported.

Jackson et al (2011)(65) compared the reactogenicity and tolerability of a booster dose of NZ-OMV vaccine given to children in the *Wong et al* 2007(68) trial that met the pre-specified definition for seroconversion (responders) with non-responders after receiving three doses of NZ-OMV vaccine. Rate of local and systemic reactions after the booster dose in both groups, were similar to those previously observed across all three doses. The most common local reaction following the booster dose was tenderness, and was reported by 91% and 83% of responders and non-responders, respectively. The most common systemic reactions following the booster dose was irritability, and was reported by 36% and 43% of responders and non-responders, respectively. The proportion of fever with axillary temperatures ≥38°C was higher among non-responders with 17% compared to 7% in the responder group. No vaccine-related serious adverse events occurred after the booster dose.

Children 2 to 17 years of age

There are currently no studies assessing the reactogenicity and tolerability of NZ-OMV vaccine in children 2 to 7 years of age or 13 to 17 years of age.

Hosking et al (2007)(66) compared the reactogenicity and tolerability of three doses of NZ-OMV vaccine produced by Chiron Vaccines (CV; now Novartis) with NZ-OMV produced by the Norwegian Institute of Public Health (NIPH), administered in children 8 to 12 years of age in a 6-week interval schedule. Rates of local reactions were similar in the two groups. The most common local reaction was pain and was reported by 98% and 95% of children after at least one dose of NZ-OMV and NIPH-NZOMV vaccines, respectively. Severe pain, defined as the inability to perform normal daily activities, was described by 7–12% of children in the NZ-OMV vaccine group following each dose. Systemic reactions after at least one dose of NZ-OMV vaccine and NIPH-NZOMV vaccine were described by 71% and 64% of children, respectively. The most common systemic reactions following at least one dose were headache and malaise, and were reported by 55% and 39% of children in the NZ-OMV vaccine group, and 44% and 42% of children in the NIPH-NZOMV group, respectively. Fever with temperatures ≥38.5°C were reported 11% of children who received at least one dose of NZ-OMV vaccine, compared to 7% of children who received NIPH-NZOMV. Compared to background school absenteeism (7.2% in 2002), probabilities of school absenteeism due to vaccination were higher in both the NZ-OMV vaccine group (16%) and the NIPH-NZOMN group (22%). A total of 5 serious adverse events occurred during this study; none were judged to be related to NZ-OMV vaccine. During the study, a total of 8 children withdrew prematurely from the study (n=5 for NZ-OMV vaccine and n=3 for NIPH-NZOMV vaccine). The most common reasons for study withdrawal were pain and dislike of phlebotomy.

Adults ≥18 years of age

There are no phase II or phase III studies assessing the reactogenicity and tolerability of NZ-OMV vaccine in adults.

Table 4: Summary of evidence related to immunogenicity of 4CMenB vaccine

Evidence related to immunogenicity of 4CMenB vaccine initiated in infants aged ≤ 12 months					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Findlow J, Borrow R, Snape MD, Dawson T, Holl, A, et al. Multicenter, open-label, randomized phase II controlled trial of an investigational recombinant Meningococcal serogroup B vaccine with and without outer membrane vesicles, administered in infancy. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2010 11;51(10): 1127-1137.	4CMenB 0.5 mL Intramuscular (IM), thigh Other infant vaccines: DPTPHib (Pediacel®; Sanofi Pasteur) at 2, 3, 4 months of age; pneumococcal conjugate vaccine (Prevenar®, Wyeth Pharmaceuticals) at 2, 4, 13 months of age; MenC conjugate vaccine (Menjugate®; Novartis) at 3, 5 months of age; MenC-Hib conjugate vaccine (Menitorix®; GSK) at 12 months of age; and MMR	Phase II RCT Parallel assignment Open label Multicenter UK NCT00381615 1º endpoint: Seroprotection, seroconversion and GMTs against reference strain one month after dose 3 2º endpoint: Seroprotection, seroconversion and GMTs against reference strain one month after dose 2 and 4	N=147 enrolled; n=46 received 4CMenB vaccine according to infant schedule Healthy 2 month old infants 4CMenB vaccine given at 2, 4, 6 and 12 months of age with other infant vaccines (n=46 infants, mean age 61.0 days, 54% male)	**Seroprotection** (per-protocol) % of subjects with hSBA titre to reference strain ≥1:4 one month after dose 2, 3 and 4: H44/76: *Dose 2*: 95% (95% CI: 82%, 99%) *Dose 3*: 87% (95% CI: 73%, 96%) *Dose 4*: 100% (95% CI: 88%, 100%) N5/99: *Dose 2*: 100% (95% CI: 89%, 100%) *Dose 3*: 95% (95% CI: 82%, 99%) *Dose 4*: 96% (95% CI: 81%, 100%) NZ98/254: *Dose 2*: 74% (95% CI: 57%, 87%) *Dose 3*: 85% (95% CI: 70%, 94%) *Dose 4*: 93% (95% CI: 77%, 99%) **Seroconversion** (per-protocol) % of subjects with ≥4-fold rise in hSBA titre to reference strain, compared with pre-vaccination baseline, one month after dose 2, 3 and 4: H44/76: *Dose 2*: 86% (95% CI: 71%, 95%) *Dose 3*: 85% (95% CI: 69%, 94%) *Dose 4*: 97% (95% CI: 83%, 100%) N5/99: *Dose 2*: 94% (95% CI: 80%, 99%) *Dose 3*: 92% (95% CI: 78%, 98%) *Dose 4*: 97% (95% CI: 83%, 100%)	Level I, Fair

Evidence related to immunogenicity of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
	(Priorix™; GSK) at 13 months of age			NZ98/254: *Dose 2*: 55% (95% CI: 38%, 71%) *Dose 3*: 78% (95% CI: 62%, 89%) *Dose 4*: 84% (95% CI: 66%, 95%) **hSBA GMTs** (per-protocol) to reference strain one month after dose 2, 3 and 4: H44/76: *Dose 2*: 28.0 (95% CI: 19.0, 40.0) *Dose 3*: 30.0 (95% CI: 19.0, 46.0) *Dose 4*: 106.0 (95% CI: 71.0, 159.0) H5/99: *Dose 2*: 104.0 (95% CI: 64.0, 169.0) *Dose 3*: 126.0 (95% CI: 77.0, 205.0) *Dose 4*: 629.0 (95% CI: 324.0, 1219.0) NZ98/254: *Dose 2*: 6.6 (95% CI: 4.8, 9.0) *Dose 3*: 19.0 (95% CI: 11.0, 33.0) *Dose 4*: 29.0 (95% CI: 15.0, 56.0)	
Snape MD, Dawson T, Oster P, Evans A, John TM, Ohene-Kena B, et al. Immunogenicity of two investigational serogroup B meningococcal vaccines in the first year of life: a randomized comparative trial. Pediatr Infect Dis J 2010 11;29(11):e71-e79.	4CMenB 0.5 mL IM, thigh Other infant vaccines: MCCV-Hib (Menitorix®; GSK) at 12 months of age in opposite thigh to study vaccine	Phase II RCT Parallel assignment Single-blind (parent/guardian) Single center UK NCT00433914 Endpoints: Seroprotection and GMTs against	N=60 enrolled; n=30 received 4CMenB vaccine Healthy 6-8 month old infants 4CMenB vaccine given at 6-8 months of age, 60 days later and 12 months of age with MCCV-Hib (n=30, mean age 7.1 months, 40.0% male)	**Seroprotection** (per-protocol) % of subjects with hSBA titre to reference strain ≥1:4 one month after dose 2 and 3: H44/76: *Dose 2*: 100% (95% CI: 85%, 100%) *Dose 3*: 100% (95% CI: 86%, 100%) N5/99: *Dose 2*: 100% (95% CI: 85%, 100%) *Dose 3*: 100% (95% CI: 86%, 100%) NZ98/254: *Dose 2*: 95% (95% CI: 77%, 100%) *Dose 3*: 96% (95% CI: 79%, 100%) **hSBA GMTs** (per-protocol) to reference strain one month after dose 2 and 3:	Level I, Fair

Evidence related to immunogenicity of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
		reference strain, and NHBA-GNA 1030 specific IgG GMCs, one month after dose 2 and 3		H44/76: *Dose 2*: 250 (95% CI: 173, 361) *Dose 3*: 189 (95% CI: 136, 263) N5/99: *Dose 2*: 534 (95% CI: 395, 721) *Dose 3*: 906 (95% CI: 700, 1172) NZ98/254: *Dose 2*: 27 (95% CI: 21, 36) *Dose 3*: 44 (95% CI: 32, 62) **ELISA IgG GMCs** (per-protocol) against NHBA-GNA1030 one month after dose 2 and 3: *Dose 2*: 2912 µg/mL (95% CI: 2178, 3894) *Dose 3*: 3521 µg/mL (95% CI: 2739, 4527)	
Prymula R, Esposito S, Kittel C, Kohl I, Toneatto D, Dull P. Prophylactic paracetamol in infants decreases fever following concomitant administration of an investigational meningococcal serogroup B vaccine with routine immunizations. Poster session presented at: 29th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); 2011 June 7-11; The Hague, Netherlands. Data on file with Novartis	4CMenB Other infant vaccines: DTaP-IPV-HBV/Hib (Infanrix-hexa®, GSK) and heptavalent pneumococcal vaccine (Prevenar®, Wyeth Pharmaceuticals) Paracetamol: 10-15 mg/kg per dose	Phase II RCT Parallel assignment Masking unclear Multicenter Argentina, Chile, Czech Republic, Hungary, Italy NCT00937521 Endpoint: percentage of subjects with	N enrolled unclear; n=367 received 4CMenB vaccine Healthy 2 month old infants 4CMenB vaccine given at 2, 3 and 4 months of age with concomitant infant vaccines (n=184 infants) 4CMenB vaccine given at 2, 3 and 4 months of age with concomitant infant	**Seroprotection** % of subjects with hSBA titres against reference strain ≥1:5 one month after dose 3 with and without paracetamol administration (95% CI not reported): H44/76 *With paracetamol*: 100% *Without paracetamol*: 100% N5/99 *With paracetamol*: 99% *Without paracetamol*: 99% NZ98/254 *With paracetamol*: 78% *Without paracetamol*: 75%	Level I, N/A (poster)

Evidence related to immunogenicity of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
		hSBA titre against reference strain ≥1:5 one month after dose 3 with and without paracetamol	vaccines and three doses of prophylactic paracetamol (one dose before vaccination and two doses separated by 4-6 hours after vaccination) (n=183 infants)		
Vesikari T, Esposito S, Kimura A, Kleinschmidt A, Ypma E, Toneatto D, et al. Immunogenicity of an investigational, multicomponent, meningococcal serogroup B vaccine in healthy infants at 2, 4, and 6 months of age. Poster session presented at: 17th International Pathogenic *Neisseria* Conference (IPNC); 2010 Sept 11-16; Banff, AB, Canada. [‡] Data on file with Novartis Vesikari T, Esposito S, Prymula R, Ypma E, Kohl I, Toneatto D, Dull P, Kimura A, for the EU Meningococcal B Infant	4CMenB Other infant vaccines: DTaP-IPV-HBV/Hib (Infanrix-hexa®, GSK) and 7-valent pneumococcal conjugate vaccine (Prevenar®, Pfizer)	Phase III RCT Parallel assignment Open label cohort Multicenter Austria, Czech Republic, Finland, Germany, Italy NCT00657709 Endpoints: Consistency of hSBA GMTs across three lots of 4CMenB, and percentage of subjects with hSBA titre against reference strain	N=3,630 enrolled; n=1,800 randomized to receive 4CMenB vaccine in cohort with immunogenicity measured, of which 1,160 were included in the primary analysis Healthy 2 month old infants 4CMenB-Lot 1 given at 2, 4 and 6 months of age with concomitant infant vaccines (n=600 infants) 4CMenB-Lot 2 given at 2, 4 and 6	All three lots of 4CMenB produced similar hSBA GMTs against reference strains H44/76, N5/99 and NZ98/254 one month after dose 3. **Seroprotection** (per-protocol) % of subjects with hSBA titre to reference strain ≥1:5 one month after dose 3 (all 4CMenB lots combined): H44/76: 100% N5/99: 100% NZ98/254: 84% M10713: 84% [‡]	Level I, Good

Evidence related to immunogenicity of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Vaccine Study Group. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccines: results of two randomised trials. The Lancet. Published online January 14th, 2013.		≥1:5 one month after dose 3	months of age with concomitant infant vaccines (n=600 infants) 4CMenB-Lot 3 given at 2, 4 and 6 months of age with concomitant infant vaccines (n=600 infants)		
Gossger N, Snape MD, Yu LM, Finn A, Bona G, Esposito S, et al. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. JAMA 2012 Feb 8;307(6):573-582.	4CMenB 0.5 mL IM, thigh Other infant vaccines: DTap-HBV-IPV/Hib (Infanrix-hexa®, GSK) and 7-valent pneumococcal glycoconjugate vaccine (Prevenar®, Wyeth Pharmaceuticals) 0.5 mL IM, opposite	Phase IIB RCT Parallel assignment Open label Multicenter Belgium, Czech Republic, Germany, Italy, Spain, UK NCT00721396 1° endpoint: Percentage of subjects with interpolated hSBA titre against reference strain ≥1:5 (LL of 95% CI ≥70%) and	N=1,885 enrolled; n=1,571 received 4CMenB vaccine Healthy 2 month old infants 4CMenB vaccine given at 2, 4 and 6 months of age with concomitant infant vaccines (n=622 infants of which 552 included in modified ITT population) 4CMenB vaccine given at 2, 4 and 6 months of age with other infant vaccines given at 3, 5 and 7 months of age (n=632 infants	Primary endpoint was met in all groups regardless of vaccine schedule, with or without concomitant routine vaccines. **Seroprotection** (modified ITT): % of subjects with hSBA titre to reference strain ≥1:5 one month after dose 3 (range among schedules): H44/76: *Dose 3*: 99.2% (95% CI: 98.1%, 99.8%) - 99.4% (95% CI: 98.4%, 99.9%) N5/99: *Dose 3*: 99.2% (95% CI: 98.0%, 99.8%) -100% (95% CI: 98.6%, 100%) NZ98/254: *Dose 3*: 79.0% (95% CI: 75.2%, 82.4%) -86.1% (95% CI: 82.9%, 89.0%) **hSBA GMTs** (modified ITT) to reference strain one month after dose 3 (range among schedules): H44/76: *Dose 3*: 82 (95% CI: 75, 91) - 110 (95% CI: 102, 119)	Level I, Fair

Evidence related to immunogenicity of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
	thigh to study vaccine	GMTs at one month after dose 3 (2, 4, 6 versus 2, 3, 4 months of age, with and without routine vaccines) 2° endpoint: Non-inferiority of concomitant schedule versus each of the other two schedules at one month after dose 3 (LL of 95% CI for difference in % of subjects with hSBA titre against reference strain ≥1:5 was greater than -10%; or LL of 95% CI for GMT ratio was >0.5 for all reference strains [post hoc])	of which 544 included in modified ITT population) 4CMenB vaccine given at 2, 3 and 4 months of age with concomitant infant vaccines (n=317 infants of which 278 included in modified ITT population) Modified ITT (intention-to-treat) population included only those who received a study vaccine and provided evaluable serum samples before and after immunization (n=1636)	N5/99: *Dose 3*: 323 (95% CI: 287, 363) - 669 (95% CI: 611, 731) NZ98/254: *Dose 3*: 11 (95% CI: 9, 12) - 17 (95% CI: 15, 19) **ELISA IgG GMCs** (per-protocol) against NHBA one month after dose 3 (range among schedules): *Dose 3*: 3211 U/mL (95% CI: 2949, 3495) - 4342 U/mL (95% CI: 4067, 4635) Non-inferiority criteria for difference in % of subjects with hSBA titre against reference strain ≥1:5 (LL of 95% CI greater than -10%) was met in all comparisons except for the concomitant group minus intercalated group for strain NZ98/254: -7.1% (95% CI: -11.7%, -2.6%). GMT ratio non-inferiority criteria (LL of 95% CI >0.5 for all reference strains) was met in all comparisons.	
Vesikari T, Prymula R, Liese J, Kollaritsch H, Bona G, Kimura A, et al. Booster dose at 12 months of an investigational meningococcal serogroup B vaccine (4CMenB) in healthy toddlers previously	4CMenB 0.5 mL Other infant vaccines: MMRV (Priorix-Tetra™, GSK)	Phase III RCT (extension study) Parallel assignment Open label Multicenter	N enrolled unclear; n=426 received 4CMenB vaccine and had blood drawn Healthy 12 month old children who	**Seroprotection** (per-protocol) % of subjects with hSBA titre to reference strain ≥1:5 one month after booster dose with (*concomitant*) and without (*separate*) MMRV vaccine (95% CI not reported): H44/76 and N5/99 *Concomitant*: 100% *Separate*: 100% NZ98/254	Level I, N/A (poster)

Evidence related to immunogenicity of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
primed at 2, 4, 6 months. Poster session presented at: 29th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); 2011 Jun 7-11; The Hague, Netherlands.		Austria, Czech Republic, Finland, Germany, Italy NCT00847145 Endpoints: Percentage of subjects in each group with hSBA titres against reference strain ≥ 1:5, hSBA GMTs against reference strain and GMT ratios of post/pre-vaccination titres.	previously received 4CMenB vaccine at 2, 4 and 6 months of age with routine vaccines 4CMenB vaccine (booster) given at 12 months of age with concomitant MMRV vaccine (n=211 children) 4CMenB vaccine (booster) given at 12 months of age with MMRV vaccine given at 13 months of age (n=215 children)	*Concomitant*: 95% *Separate*: 94% M10713 *Concomitant*: 97.5% *Separate*: 97.5% **hSBA GMTs** (per-protocol) to reference strain one month after booster dose with (*concomitant*) and without (*separate*) MMRV vaccine: H44/76 *Concomitant*: 139 (95% CI: 123, 156) *Separate*: 119 (95% CI: 105, 133) N5/99 *Concomitant*: 1503 (95% CI: 1339, 1686) *Separate*: 1429 (95% CI: 1274, 1603) NZ98/254 *Concomitant*: 39 (95% CI: 33, 46) *Separate*: 32 (95% CI: 27, 37) M10713 *Concomitant*: 41 (95% CI: 32, 54) *Separate*: 43 (95% CI: 34, 54) **hSBA GMT ratios** (per-protocol) of post to pre-booster titres against reference strain with (*concomitant*) and without (*separate*) MMRV vaccine: H44/76 *Concomitant*: 13 (95% CI: 12, 14) *Separate*: 11 (95% CI: 10, 13) N5/99 *Concomitant*: 18 (95% CI: 16, 21) *Separate*: 18 (95% CI: 16, 20) NZ98/254 *Concomitant*: 19 (95% CI: 16, 22)	

Evidence related to immunogenicity of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				Separate: 15 (95% CI: 12, 17) M10713 *Concomitant*: 5.2 (95% CI: 3.7, 7.6) *Separate*: 5.3 (95% CI: 3.8, 7.4)	
Kimura A, Vesikari T, Prymula R, Liese J, Dull P. Persistence of the immune response to an investigational multicomponent meningococcal serogroup B (4CMenB) vaccine following priming in infants or toddlers. Poster session presented at: 7th World Congress of the World Society for Pediatric Infectious Diseases (WSPID); 2011 Nov 16-19; Melbourne, Australia.	4CMenB 0.5 mL	Phase II/III RCT (extension study) Parallel assignment Open label Multicenter Czech Republic, Finland NCT01139021 Endpoint: Percentage of subjects with hSBA titre against reference strain ≥1:5 twelve months after dose 4	N=508 enrolled; n=300 received 4CMenB vaccine Healthy 23 to 27 month old children who previously received 4CMenB vaccine at 2, 4, 6 and 12 months of age with routine vaccines (n=300 children)	**Seroprotection**, % of subjects with hSBA titres against reference strain ≥1:5 twelve months after dose 4 (95% CI not reported): H44/76 *12 months after dose 4*: 62% N5/99 *12 months after dose 4*: 97% NZ98/254 *12 months after dose 4*: 17%	Level I, N/A (poster)
Saroey P, Snape MD, John TM, Robinson H, Kelly S, Gossger N, Wang H, Toneatto D, Dull PM, A Kimura A, Pollard AJ Persistence of bacterial antibody following early infant immunization with serogroup B	4CMenB 0.5 mL IM, thigh	Follow-on phase 2, open labelled, single centre randomised study UK NCT01027351	113 participants were recruited for follow-on study, of whom 70 were from the original study and 43 were Men B vaccine naïve for comparison ("control", shown in	**Group 4CMenB-2,4,6,12** **Seroprotection**, % of subjects with hSBA titres ≥ 1:4 against reference strain prior to (age 40 months) and one month after booster(Dose 5) 44/76-SL Prior to 5th dose: 65 (95% CI: 39, 87)	Level I NA (poster)

Evidence related to immunogenicity of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
meningococcal vaccine and immunogenicity of pre-school booster doses- A follow on study. European Society for Paediatric Infectious Diseases (ESPID); 2012, 08-12 May, Thessaloniki, Greece Snape MD, John TM, Robinson H, Kelly S, Gossger N, Wang H, Toneatto D, Dull PM, Kimura A, Pollard AJ. Persistence of bactericidal antibodies following early infant immunization with investigational serogroup B meningococcal vaccines and immunogenicity of preschool booster doses International Pathogenic Neisseria Conference (IPNC); 2012, 09-14 September, Würzburg, Germany		Endpoints: Percentage of participants with hSBA titres ≥ 1:4 for four reference strains at 40 months (persistence) and 41 months +/- 43 months (booster responses)	immunogenicity in 2-10 yo section) Group 4CMenB-2,4,6,12) received 4 doses of 4CMenB vaccine at 2,4,6 and 12 months in early infant study n=19 For this study, they were given a booster dose at 40 months (Group 4CMenB-12) Received 1 dose of 4CMenB vaccine at 12 months in early infant study. n=8 For this study, they were given 2 boosters at 40 and 42 months of age	Dose 5: 100 (95% CI: 82, 100) N5/99 Prior to 5th dose:: 75 (95% CI: 50, 90) Dose 5: 100 (95% CI: 81, 100) NZ 98/254 Prior to 5th dose:: 41 (95% CI: 18, 70) Dose 5: 90 (95% CI: 68, 99) M10713 Prior to 5th dose:: 63 (95% CI: 4, 90) Dose 5: 95 (95% CI: 70, 100) **Group 4CMenB-12** **Seroprotection**, % of subjects with hSBA titres ≥ 1:4 against reference strain prior to (age 40 months) , one month after first booster (Dose 2), and one month after second booster(Dose 3) 44/76-SL Prior to 2nd dose: 38 (95% CI: 10, 78) Dose 2: 100 (95% CI: 59, 100) Dose 3: 100 (95% CI: 62, 100) N5/99 Prior to 2nd dose: 0 (95% CI: 0 38) Dose 2: 100 (95% CI: 60, 100) Dose 3: 100 (95% CI: 63, 100)	

Evidence related to immunogenicity of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				NZ 98/254 Prior to 2^{nd} dose: 0 (95% CI: 0, 38) Dose 2: 100 (95% CI: 60, 100) Dose 3: 100 (95% CI: 62, 100) M10713 Prior to 2^{nd} dose: 27 (95% CI: 2, 65) Dose 2: 87 (95% CI: 41, 100) Dose 3: 100 (95% CI: 62, 100)	
Snape MD, Saroey P, John TM, Robinson H, Kelly S, Gossger N, Yu LM, Wang H, Toneatto D, Dull PM, Pollard AJ Persistence of bacterial antibody following early infant vaccination with a serogroup B meningococcal vaccine and immunogenicity of a preschool booster dose. Canadian Medical Association Journal; 2013; 185(15)	4CMenB 0.5 mL IM, thigh	Follow-on phase 2, open labelled, randomised study UK NCT01027351 Endpoints: Percentage of participants with hSBA titres ≥ 1:4 for four reference strains at 40 months (persistence) and 41 months +/- 43 months (booster responses)	190 participants enrolled the follow-on study, of whom 147 were from the original study and 43 were Men B vaccine naïve for comparison Group 4CMenB-2,4,6,12) received 4 doses of 4CMenB vaccine at 2,4,6 and 12 months in early infant study n=19 For this study, they were given a booster dose at 40 months Group 4CMenB-12 Received 1 dose of	**Group 4CMenB-2,4,6,12** **Seroprotection**, % of subjects with hSBA titres ≥ 1:4 against reference strain prior to (age 40 months) and one month after booster(Dose 5) 44/76-SL Prior to 5^{th} dose: 65 (95% CI: 38, 86) Dose 5: 100 (95% CI: 82, 100) N5/99 Prior to 5^{th} dose:: 76 (95% CI: 50, 93) Dose 5: 100 (95% CI: 81, 100) NZ 98/254 Prior to 5^{th} dose:: 41 (95% CI: 18, 67) Dose 5: 89 (95% CI: 67, 99) M10713 Prior to 5^{th} dose:: 67 (95% CI: 38, 88) Dose 5: 94 (95% CI: 73, 100) **Group 4CMenB-12**	Level I Fair

Evidence related to immunogenicity of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
			4CMenB vaccine at 12 months in early infant study. n=14 For this study, they were given 2 boosters at 40 and 42 months of age Control 4CMenB group received 2 doses of 4CMenB vaccine at 40 and 42 months of age	**Seroprotection**, % of subjects with hSBA titres ≥ 1:4 against reference strain prior to (age 40 months) , one month after first booster (Dose 2), and one month after second booster(Dose 3) 44/76-SL Prior to 2nd dose: 38 (95% CI: 9, 76) Dose 2: 100 (95% CI: 59, 100) Dose 3: 100 (95% CI: 63, 100) N5/99 Prior to 2nd dose: 0 (95% CI: 0, 37) Dose 2: 100 (95% CI: 59, 100) Dose 3: 100 (95% CI: 63, 100) NZ 98/254 Prior to 2nd dose: 0 (95% CI: 0, 37) Dose 2: 100 (95% CI: 59, 100) Dose 3: 100 (95% CI: 63, 100) M10713 Prior to 2nd dose: 27 (95% CI: 3, 65) Dose 2: 87 (95% CI: 42, 100) Dose 3: 100 (95% CI: 63, 100) **Control 4CMenB** **Seroprotection**, % of subjects with hSBA titres ≥ 1:4 against reference strain prior to, one month after first dose (Dose 1) and one month after second dose (Dose 2) 44/76-SL Prior to 1st dose: 63 (95% CI: 46, 77)	

Evidence related to immunogenicity of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				Dose 1: 89 (95% CI: 75, 97) Dose 2: 100 (95% CI: 90, 100) N5/99 Prior to 1st dose: 3 (95% CI: 0, 13) Dose 1: 76 (95% CI: 60, 89) Dose 2: 100 (95% CI: 903, 100) NZ 98/254 Prior to 1st dose: 0 (95% CI: 0, 9) Dose 1: 66 (95% CI: 49, 80) Dose 2: 94 (95% CI: 81, 99) M10713 Prior to 1st dose: 68 (95% CI: 51, 81) Dose 1: 76 (95% CI: 60, 89) Dose 2: 89 (95% CI: 74, 97	
Philip J, Snape MD, Robinson H, Kelly S, Pollard AJ, John TM, Gossger N, Toneatto D, Kittel C, Kimura A, Dull PM. Bacterial antibody persistence two years following meningococcal B vaccination at 6,8,12 months in 40 month old children. European Society for Paediatric Infectious Diseases (ESPID); 2012, 08-12 May, Thessaloniki, Greece	4CMenB 0.5 mL IM, thigh	Phase II RCT Parallel assignment Single-blind (parent/guardian) Single center UK NCT01026974 Endpoints: Percentage of participants with hSBA titres ≥ 1:4 for four reference	4CMenB group received 4CMenB at 6, 8 and 12 months in the original study. This is an extension of the original study: 4CMenB group n=14 enrolled and received a fourth/booster dose of 4CMenB at 40 months of age.	**4CMenB group** **Seroprotection**, % of subjects with hSBA titres ≥ 1:4 against reference strain prior to (age 40 months) and one month after booster (Dose 4) 44/76-SL Prior to 4th dose: 35 (95% CI: 12, 65) Dose 4: 100 (95% CI: 77, 100) N5/99 Prior to 4th dose :100 (95% CI: 77, 100) Dose 4: 100 (95% CI: 77, 100) NZ 98/254 Prior to 4th dose: 14 (95% CI: 2, 43) Dose 4: 93 (95% CI: 66, 100)	Level I NA (poster)

Evidence related to immunogenicity of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Snape MD, Robinson H, Kelly S, Pollard AJ, John TM, Gossger N, Toneatto D, Kittel C, Kimura A, Dull PM. Bacterial antibody persistence two years following meningococcal B vaccination at 6,8,12 months in 40 month old children. International Pathogenic Neisseria Conference (IPNC); 2012, 09-14 September, Würzburg, Germany.		strains at 40 months (persistence), 41 Months and 43 months.	Blood samples were taken at enrolment (40 months) and 41 months (one month post booster).	M10713 Prior to 4th dose: 79 (95% CI: 49, 95) Dose 4: 92 (95% CI: 65, 100)	

Evidence related to immunogenicity of 4CMenB vaccine initiated in children aged 12 to 24 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Findlow J, Borrow R, Snape MD, Dawson T, Holl, A, et al. Multicenter, open-label, randomized phase II controlled trial of an investigational recombinant Meningococcal serogroup B vaccine with and without outer membrane vesicles, administered in infancy. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2010 11;51(10):1127-1137.	4CMenB 0.5 mL IM, thigh Other infant vaccines: DPTPHib (Pediacel®; Sanofi Pasteur) at 2, 3, 4 months of age; pneumococcal conjugate vaccine (Prevenar®, Wyeth Pharmaceuticals) at 2, 4, 13 months of age; MenC conjugate vaccine (Menjugate®; Novartis) at 3, 5 months of age; MenC-Hib conjugate vaccine (Menitorix®; GSK) at 12 months of age; and MMR (Priorix™; GSK) at 13 months of age	Phase II RCT Parallel assignment Open label Multicenter UK NCT00381615 Endpoints: Seroprotection, seroconversion and GMTs against reference strain one month after dose 1 at 12 months of age	n=147 enrolled; n=23 received 4CMenB vaccine Healthy 12 month old children 4CMenB vaccine given at 12 months of age with other infant vaccines (n=23 children, mean age 60.7 days, 55 to 79 days, 74% male)	**Seroprotection** (per-protocol) % of subjects with hSBA titre to reference strain ≥1:4 one month after dose 1: H44/76 *Dose 1*: 73% (95% CI: 50%, 89%) N5/99 *Dose 1*: 73% (95% CI: 50%, 89%) NZ98/254 *Dose 1*: 18% (95% CI: 5%, 40%) **Seroconversion** (per-protocol) % of subjects with ≥4-fold rise in hSBA titre to reference strain, compared with pre-vaccination baseline, one month after dose 1: H44/76 *Dose 1*: 36% (95% CI: 17%, 59%) N5/99 *Dose 1*: 59% (95% CI: 36%, 79%) NZ98/254 *Dose 1*: 9% (95% CI: 1%, 29%) **hSBA GMT** (per-protocol) to reference strain one month after dose 1: 44/76-SL *Dose 1*: 6.0 (95% CI: 3.5, 10.0) 5/99 *Dose 1*: 8.0 (95% CI: 4.2, 15.0) NZ98/254 *Dose 1*: 1.7 (95% CI: 1.1, 2.5)	Level I, Fair

Evidence related to immunogenicity of 4CMenB vaccine initiated in children aged 12 to 24 months

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Prymula R, Vesikari T, Esposito S, Kohl I, Ypma E, Kleinschmidt A, et al. Catch-up vaccination of healthy toddlers with an investigational multicomponent meningococcal serogroup B vaccine (4CMenB) – exploration of a two-dose schedule. Poster session presented at: 29th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); 2011 Jun 7-11; The Hague, Netherlands.	4CMenB 0.5 mL MMRV (Priorix-Tetra™, GSK)	Phase III RCT (extension study) Parallel assignment Open label Multicenter Austria, Czech Republic, Finland, Germany, Italy NCT00847145 Endpoints: Percentage of subjects in each group with hSBA titres against reference strain ≥ 1:5, hSBA GMTs against reference strain and GMT ratios of post/pre-vaccination titres	N enrolled unclear; n=230-232 received 4CMenB vaccine and had blood drawn Healthy 12 month old children 4CMenB vaccine given at 12 and 14 months of age (dose 1 and 2) with MMRV vaccine given at 12 months of age (n=67-68 children) 4CMenB vaccine given at 13 and 15 months of age (dose 1 and 2) with MMRV vaccine given at 12 months of age (n=163-164 children)	**Seroprotection** (per-protocol) % of subjects with hSBA titre to reference strain ≥1:5 one month after dose 2, at 14 and 15 months of age, respectively (95% CI not reported): H44/76 and N5/99 *Dose 2 (14 mos.)*: 100% *Dose 2 (15 mos.)*: 100% NZ98/254 *Dose 2 (14 mos.)*: 100% *Dose 2 (15 mos.)*: 96% **hSBA GMTs** (per-protocol) to reference strain one month after dose 2, at 14 and 15 months of age, respectively: H44/76 *Dose 2 (14 mos.)*: 271 (95% CI: 237, 310) *Dose 2 (15 mos.)*: 248 (95% CI: 201, 306) N5/99 *Dose 2 (14 mos.)*: 599 (95% CI: 520, 690) *Dose 2 (15 mos.)*: 627 (95% CI: 502, 783) NZ98/254 *Dose 2 (14 mos.)*: 43 (95% CI: 38, 49) *Dose 2 (15 mos.)*: 32 (95% CI: 26, 40) **hSBA GMT ratios** (per-protocol) of post to pre-vaccination titres against reference strain one month after dose 2, at 14 and 15 months of age, respectively: H44/76 *Dose 2 (14 mos.)*: 217 (95% CI: 185, 255) *Dose 2 (15 mos.)*: 203 (95% CI: 158, 261)	Level I, N/A (poster)

Evidence related to immunogenicity of 4CMenB vaccine initiated in children aged 12 to 24 months					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				N5/99 *Dose 2 (14 mos.)*: 560 (95% CI: 478, 656) *Dose 2 (15 mos.)*: 620 (95% CI: 485, 793) NZ98/254 *Dose 2 (14 mos.)*: 43 (95% CI: 37, 49) *Dose 2 (15 mos.)*: 31 (95% CI: 25, 38) **ELISA IgG GMCs** (per-protocol) for NHBA one month after dose 2, at 14 and 15 months of age, respectively (units not reported): *Dose 2 (14 mos.)*: 5698 (95% CI: 5030, 6454) *Dose 2 (15 mos.)*: 7154 (95% CI: 5880, 8704) **ELISA ratios** of post to pre-vaccination (per-protocol) for NHBA one month after dose 2, at 14 and 15 months of age, respectively (units not reported): *Dose 2 (14 mos.)* :279 (95% CI: 245, 317) *Dose 2 (15 mos.)*: 326 (95% CI: 259, 410)	
Kimura A, Vesikari T, Prymula R, Liese J, Dull P. Persistence of the immune response to an investigational multicomponent meningococcal serogroup B	4CMenB 0.5 mL	Phase II/III RCT (extension study) Parallel assignment Masking unclear Multicenter Czech Republic, Finland	N=508 enrolled; n=86 received 4CMenB vaccine Healthy 23 to 27 month old children who previously received 2 doses of	**Seroprotection**, % of subjects with hSBA titres against reference strain ≥1:5 twelve months after dose 2 (95% CI not reported): H44/76 *12 months after dose 2*: 70% ‡ N5/99 *12 months after dose 2*: 96% ‡ NZ98/254 *12 months after dose 2*: 15% ‡	Level I, N/A (poster)

Evidence related to immunogenicity of 4CMenB vaccine initiated in children aged 12 to 24 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
(4CMenB) vaccine following priming in infants or toddlers. Poster session presented at: 7th World Congress of the World Society for Pediatric Infectious Diseases (WSPID); 2011 Nov 16-19; Melbourne, Australia. ‡ Data on file with Novartis		NCT01139021 Endpoint: Percentage of subjects in each group with hSBA titre against reference strain ≥1:5 twelve months after the last dose of 4CMenB vaccine	4CMenB vaccine given at 12, 14 or 13, 15 months of age 4CMenB vaccine given at 24 months of age (n=86 children)	100% of subjects achieved hSBA titres ≥1:5 against each of the three strains one month after dose 3.	

Evidence related to immunogenicity of 4CMenB vaccine initiated in adolescents aged 2 to 10 years

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Saroey P, Snape MD, John TM, Robinson H, Kelly S, Gossger N, Wang N, Toneatto D, Dull PM, Kimura A, Pollard AJ Persistence of bacterial antibody following early infant immunization with serogroup B meningococcal vaccine and immunogenicity of pre-school booster doses- A follow on study. European Society for Paediatric Infectious Diseases (ESPID); 2012, 08-12 May, Thessaloniki, Greece Snape MD, John TM, Robinson H, Kelly S, Gossger N, Wang H, Toneatto D, Dull PM, Kimura A, Pollard AJ. Persistence of bactericidal antibodies following early infant immunization with investigational serogroup B meningococcal vaccines and immunogenicity of preschool booster doses International Pathogenic Neisseria Conference (IPNC); 2012,	4CMenB 0.5 mL IM, thigh	Follow-on phase 2, open labelled, single centre randomised study UK NCT01027351 Endpoints: Percentage of participants with hSBA titres ≥ 1:4 for four reference strains at 40 months (prior to immunization), 41 Months (one month after first dose) and 43 months (one month after second dose).	4CMenB group n=43 4CMenB naïve children who received 2 doses of 4CMenB vaccine at 40 and 42 months of life (referred to in this study as "control" group as were compared to children previously immunized in infancy)	**Seroprotection**, % of subjects with hSBA titres ≥ 1:4 against reference strain prior to first dose (baseline) , one month after first dose (Dose 1), and one month after the second dose (Dose 2). 44/76-SL Baseline: 62 (95% CI: 47, 78) Dose 1: 90 (95% CI: 75, 98) Dose2 :100 (95% CI: 95, 100) 5/99 Baseline: 0 (95% CI: 0, 5) Dose 1: 75 (95% CI: 60, 90) Dose2 :100 (95% CI: 90, 100) NZ 98/254 Baseline: 0 (95% CI:0, 10) Dose 1: 65 (95% CI: 50, 80) Dose2 :92 (95% CI: 80, 98) M10713 Baseline:70 (95% CI: 50, 81) Dose 1: 75 (95% CI: 60, 90) Dose2 : 90 (95% CI: 75, 98)	Level I NA (poster)

Evidence related to immunogenicity of 4CMenB vaccine initiated in adolescents aged 2 to 10 years

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
09-14 September, Würzburg, Germany					
Philip J, Snape MD, Robinson H, Kelly S, Pollard AJ John TM, Gossger N, Toneatto D, Kittel C, Kimura A, Dull PM. Bacterial antibody persistence two years following meningococcal B vaccination at 6,8,12 months in 40 month old children. European Society for Paediatric Infectious Diseases (ESPID); 2012, 08-12 May, Thessaloniki, Greece M.D. Snape MD, Robinson H, Kelly S, Pollard AJ, John TM, Gossger N, Toneatto D, Kittel C, Kimura A, Dull P.M. Bacterial antibody persistence two years following meningococcal B vaccination at 6,8,12 months in 40 month old children. International Pathogenic Neisseria Conference	4CMenB 0.5 mL IM, thigh Recombinant-proteins alone (rMenB)	Phase II RCT Parallel assignment Single-blind (parent/guardian) Single center UK NCT01026974 Endpoints: Percentage of participants with hSBA titres ≥ 1:4 for four reference strains at 40 months (prior to immunization), 41 months (after first dose) and 43 months (after second dose).	4CMenB group n=41 4CMenB vaccine naïve age-matched received two doses of 4CMenB approximately 60 days apart. (at enrolment and at 42 months) Referred to as "control" group as were age-matched and compared to participants immunized in infancy. Blood samples were taken at enrolment and 30 days after each immunization.	**Seroprotection**, % of subjects with hSBA titres ≥ 1:4 against reference strain at baseline prior to first dose (age 40 months) , one month after first dose (Dose 1), and one month after the second dose (Dose 2). 44/76-SL baseline: 2 (95% CI: 0, 12) Dose 1: 71 (95% CI: 55, 85) Dose 2: 100 (95% CI: 98, 100) 5/99 baseline: N/A Dose 1: 85 (95% CI: 73, 95) Dose 2: 100 (95% CI: 89, 100) NZ 98/254 baseline: 53 (95% CI: 36, 68) Dose 1: 62 (95% CI: 45, 77) Dose 2: 100 (95% CI: 88, 100) M10713 baseline: 52 (95% CI: 35, 68) Dose 1: 62 (95% CI: 45, 77) Dose 2: 71 (95% CI: 53, 87)	Level I NA (poster)

Evidence related to immunogenicity of 4CMenB vaccine initiated in adolescents aged 2 to 10 years

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
(IPNC); 2012, 09-14 September, Würzburg, Germany.					

Evidence related to immunogenicity of 4CMenB vaccine initiated in adolescents aged 11 to 17 years

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Santolaya ME, O'Ryan ML, Valenzuela MT, Prado V, Vergara R, Munoz A, et al. Immunogenicity and tolerability of a Multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study. Lancet 2012 Feb 18;379(9816):617-624.	4CMenB 0.5 mL IM, arm Placebo: 1.5 mg aluminum hydroxide, 10 mM histidine, 110-120 mM saline 0.5 mL IM, arm	Phase IIb/III RCT Parallel assignment Single-blind (observer) Multicenter Chile NCT00661713 Endpoints: LL of 95% CI for % of subjects with interpolated hSBA titre ≥1:4 one month after 1st, 2nd or 3rd dose of 4CMenB was 85% or higher for strains with an expected response of 95%, and 75% or higher for a strain with an expected response of 85%; GMTs, computed controlling for vaccine group and study center	N=1,631 enrolled and received 4CMenB vaccine Healthy 11 to 17 year old adolescents Four injections at 0, 1, 2, 6 month time points of either 4CMenB vaccine or placebo; at 6 months, subjects in arms 1-3 received either 4CMenB vaccine or placebo (1:2 ratio), arm 4 received placebo, and arm 5 received 4CMenB vaccine: 4CMenB vaccine given at 0 or 0, 6 months with placebo given at 1, 2, 6 or 1, 2 months (n=375, mean age 13.8 years, 1.9 SD, 41% male) 4CMenB vaccine given at 0, 1 or 0, 1, 6 months with	Seroprotection endpoint was met in each group with the exception of the 0, 2, 6 month schedule at one month after dose 1 against strain H44/76: 90% (95% CI: 83%, 95%). **hSBA GMTs** (per-protocol) to reference strain one month after dose 2 and 3 (within the 3-dose schedules): H44/76 *0, 1, 2 month schedule* *Dose 2*: 193 (95% CI: 164, 228) *Dose 3*: 240 (95% CI: 205, 280) *0, 1, 6 month schedule* *Dose 2*: 182 (95% CI: 138, 240) *Dose 3*: 324 (95% CI: 236, 443) *0, 2, 6 month schedule* *Dose 2*: 182 (95% CI: 139, 236) *Dose 3*: 259 (95% CI: 188, 357) N5/99 *0, 1, 2 month schedule* *Dose 2*: 481 (95% CI: 415, 556) *Dose 3*: 584 (95% CI: 510, 668) *0, 1, 6 month schedule* *Dose 2*: 505 (95% CI: 396, 644) *Dose 3*: 1094 (95% CI: 849, 1410) *0, 2, 6 month schedule* *Dose 2*: 540 (95% CI: 431, 677) *Dose 3*: 994 (95% CI: 767, 1289) NZ98/254 *0, 1, 2 month schedule* *Dose 2*: 92 (95% CI: 77, 110) *Dose 3*: 122 (95% CI: 102, 145)	Level I, Fair

Evidence related to immunogenicity of 4CMenB vaccine initiated in adolescents aged 11 to 17 years

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
			placebo given at 2, 6 or 2 months (n=375, mean age 13.9 years, 1.9 SD, 43% male) 4CMenB vaccine given at 0, 2 or 0, 2, 6 months with placebo given at 1, 6 or 1 months (n=380, mean age 13.7 years, 1.9 SD, 44% male) 4CMenB vaccine given at 0, 1, 2 months with placebo given at 6 months (n=373, mean age 13.8 years, 1.9 SD, 47% male) 4CMenB vaccine given at 6 months with placebo given at 0, 1, 2 months (n=128, mean age 13.8 years, 2.0 SD, 48% male)	*0, 1, 6 month schedule* *Dose 2*: 98 (95% CI: 72, 132) *Dose 3*: 181 (95% CI: 132, 248) *0, 2, 6 month schedule* *Dose 2*: 117 (95% CI: 87, 157) *Dose 3*: 168 (95% CI: 122, 232) **hSBA GMTs** (per-protocol) to reference strain one month after dose 1 and 2 (within the 2-dose schedules): H44/76 *0, 1 month schedule* *Dose 2*: 52 (95% CI: 41, 65) *Dose 3*: 187 (95% CI: 154, 228) *0, 2 month schedule* *Dose 2*: 57 (95% CI: 45, 71) *Dose 3*: 230 (95% CI: 191, 277) *0, 6 month schedule* *Dose 2*: 46 (95% CI: 33, 63) *Dose 3*: 218 (95% CI: 157, 302) N5/99 *0, 1 month schedule* *Dose 2*: 72 (95% CI: 59, 68) *Dose 3*: 451 (95% CI: 381, 535) *0, 2 month schedule* *Dose 2*: 76 (95% CI: 62, 93) *Dose 3*: 822 (95% CI: 702, 964) *0, 6 month schedule* *Dose 2*: 81 (95% CI: 61, 109) *Dose 3*: 880 (95% CI: 675, 1147) NZ98/254 *0, 1 month schedule*	

Evidence related to immunogenicity of 4CMenB vaccine initiated in adolescents aged 11 to 17 years

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				Dose 2: 45 (95% CI: 36, 55) *Dose 3*: 89 (95% CI: 72, 110) *0, 2 month schedule* *Dose 2*: 42 (95% CI: 34, 52) *Dose 3*: 125 (95% CI: 102, 154) *0, 6 month schedule* *Dose 2*: 42 (95% CI: 31, 56) *Dose 3*: 140 (95% CI: 101, 195) **ELISA IgG GMC**, µg/mL (per-protocol) against NHBA-GNA 1030 one month after dose 2 and 3 (within the 3-dose schedules): *0, 1, 2 month schedule* *Dose 2*: 3693 (95% CI: 2459, 5546) *Dose 3*: 5314 (95% CI: 3599, 7845) *0, 1, 6 month schedule* *Dose 2*: 3025 (95% CI: 2015, 4543) *Dose 3*: 3840 (95% CI: 2386, 6179) *0, 2, 6 month schedule* *Dose 2*: 3332 (95% CI: 2257, 4919) *Dose 3*: 5492 (95% CI: 34136, 8837) **ELISA IgG GMC**, µg/mL (per-protocol) against NHBA-GNA 1030 one month after dose 1 and 2 (within the 2-dose schedules): *0, 1 month schedule* *Dose 2*: 217 (95% CI: 130, 361) *Dose 3*: 3875 (95% CI: 2565, 5855) *0, 2 month schedule* *Dose 2*: 220 (95% CI: 132, 366) *Dose 3*: 2936 (95% CI: 1989, 4335) *0, 6 month schedule* *Dose 2*: 194 (95% CI: 117, 323) *Dose 3*: 2087 (95% CI: 1297, 3357)	

Evidence related to immunogenicity of 4CMenB vaccine initiated in adolescents aged 11 to 17 years

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Santolaya ME, O'Ryan ML, Valenzuela MT, Prado V, Vergara R, Munoz A, et al. Persistence of antibodies in adolescents 18-24 month after immunization with one, two or three doses of 4CMenB meningococcal serogroup B vaccine. Hum Vaccin Immunother. 2013 Nov 9(11): 2304–2310.	4CMenB 0.5 mL IM, arm	Follow-on phase IIb/III, RCT Parallel assignment Single-blind (observer) Multicenter Chile NCT01148524 Endpoints: hSBA titre ≥1:4 and GMTs 18-24 months after 1st, 2nd or 3rd dose of 4CMenB	N=666 adolescents that previously received at least one dose of 4CMenB vaccine N=151 newly recruited vaccine-naïve controls 13-19 years of age	**Seroprotection**, % of subjects with hSBA titres against reference strain ≥1:4 18-24 months following last dose of one dose schedule given at month 0 or 6 (Schedule 1); two dose schedule given at months 0/1, 0/2, or 0/6 (Schedule 2), three dose schedule given at 0/1/2, or 0/1/6 or 0/2/6 schedule (Schedule 3); and % of subjects with hSBA titres against reference strain ≥1:4 in vaccine naïve group (Control) H44/76 *Schedule 1:* 73 (95% CI: 65, 80) *Schedule 2:* 82 (95% CI: 77, 87) *Schedule 3:* 86 (95% CI: 81, 90) *Control:* 50 (95% CI: 42, 59) N5/99 *Schedule 1:* 68 (95% CI: 60, 75) *Schedule 2:* 94 (95% CI: 91, 97) *Schedule 3:* 97 (95% CI: 95, 99) *Control:* 25 (95% CI: 18, 33) NZ98/254 *Schedule 1:* 62 (95% CI: 53, 70 *Schedule 2:* 77 (95% CI: 71, 82) *Schedule 3:* 90 (95% CI: 86, 94) *Control:* 40 (95% CI: 32, 48) **hSBA GMTs** (per-protocol) against three strains 18-24 months after last dose of one dose schedule given at month 0 or 6 (Schedule 1); two dose schedule given at months 0/1, 0/2, or 0/6 (Schedule 2) or three dose schedule given at 0/1/2, 0/1/6 or 0/2/6 schedule (Schedule 3); and vaccine naïve group (Control)	Level I, Fair

Evidence related to immunogenicity of 4CMenB vaccine initiated in adolescents aged 11 to 17 years					
STUDY DETAILS					SUMMARY
Study	Vaccine	Study Design	Participants	Summary of Key Findings Using Text or Data	Level and Quality of Evidence
				H44/76 *Schedule 1:* 17 (95% CI: 12, 23) *Schedule 2:* 31 (95% CI: 24, 39) *Schedule 3:* 44 (95% CI: 35, 55) *Control:* 4.5 (95% CI: 3.5, 5.8) N5/99 *Schedule 1:* 8 (95% CI: 6.2, 10) *Schedule 2:* 46 (95% CI: 38, 55) *Schedule 3:* 86 (95% CI: 72, 104) *Control:* 2.1 (95% CI: 1.7, 2.6) NZ98/254 *Schedule 1:* 8.9 (95% CI: 6.7, 12) *Schedule 2:* 20 (95% CI: 16, 24) *Schedule 3:* 30 (95% CI: 24, 37) *Control:* 3.2 (95% CI: 2.5, 4.1)	

Evidence related to immunogenicity of 4CMenB vaccine initiated in adults aged 18 to 55 years

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Kimura A, Toneatto D, Kleinschmidt A, Wang H, Dull P. Immunogenicity and safety of a multicomponent meningococcal serogroup B vaccine and a quadrivalent meningococcal CRM197 conjugate vaccine against serogroups A, C, W-135, and Y in adults who are at increased risk for occupational exposure to meningococcal isolates. Clin Vaccine Immunol 2011 Mar;18(3):483-486.	4CMenB 0.5 mL IM, arm	Phase II Single arm study Open label Multicenter Germany, Italy NCT00560313 Endpoints: Percentage of subjects with hSBA titre against reference strain ≥1:4, percentage of subjects with 4-fold rise in hSBA titres against reference strain (compared to baseline) and GMTs	N=54 enrolled and received 4CMenB vaccine, of which 25-46 met criteria for immunogenicity analysis Healthy 18 to 50 year old laboratory workers 4CMenB vaccine given at 0, 2, 6 month time points (n=54, mean age 31.8 years, 6.1 SD, 50% male)	**Seroprotection** (per-protocol) % of subjects with hSBA titre to reference strain ≥1:4 one month after dose 1, 2 and 3: H44/76 *Dose 1*: 84% (95% CI: 64%, 95%) *Dose 2*: 100% (95% CI: 92%, 100%) *Dose 3*: 97% (95% CI: 87%, 100%) N5/99 *Dose 1*: 88% (95% CI: 69%, 97%) *Dose 2*: 100% (95% CI: 92%, 100%) *Dose 3*: 100% (95% CI: 91%, 100%) NZ98/254 *Dose 1*: 80% (95% CI: 59%, 93%) *Dose 2*: 91% (95% CI: 79%, 98%) *Dose 3*: 92% (95% CI: 79%, 98%) **Seroconversion** (per-protocol) % of subjects with a 4-fold rise in hSBA titres against reference strain one month after dose 1, 2 and 3, compared to baseline: H44/76 *Dose 1*: 80% (95% CI: 59%, 93%) *Dose 2*: 100% (95% CI: 92%, 100%) *Dose 3*: 92% (95% CI: 79%, 98%) N5/99 *Dose 1*: 64% (95% CI: 43%, 82%) *Dose 2*: 100% (95% CI: 92%, 100%) *Dose 3*: 100% (95% CI: 91%, 100%) NZ98/254 *Dose 1*: 68% (95% CI: 46%, 85%) *Dose 2*: 78% (95% CI: 64%, 89%) *Dose 3*: 69% (95% CI: 52%, 83%)	Level II-1, Fair

Evidence related to immunogenicity of 4CMenB vaccine initiated in adults aged 18 to 55 years

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				hSBA GMTs (per-protocol) to reference strain one month after dose 1, 2 and 3: H44/76 *Dose 1*: 33 (95% CI: 15, 72) *Dose 2*: 93 (95% CI: 71, 121) *Dose 3*: 95 (95% CI: 68, 131) N5/99 *Dose 1*: 29 (95% CI: 14, 60) *Dose 2*: 144 (95% CI: 108, 193) *Dose 3*: 269 (95% CI: 205, 354) NZ98/254 *Dose 1*: 23 (95% CI: 11, 49) *Dose 2*: 32 (95% CI: 21, 48) *Dose 3*: 30 (95% CI: 18, 50)	
Findlow J, Bai X, Findlow H, Newton E, Kaczmarski E and Borrow R. Safety and immunogenicity of a four component meningococcal group B vaccine (4CMenB) and a quadrivalent meningococcal group A, C, W135 and Y conjugate vaccine (Menveo) in UK laboratory workers with potential occupational exposure to meningococci. International Pathogenic Neisseria Conference (IPNC); 2012, 09-14 September, Würzburg, Germany.	4CMenB Quadrivalent group A, C, W135 and Y conjugate vaccine (Menveo®, Novartis).	Phase II trial Single arm study UK NCT00962624 Endpoints: Proportions of subjects with hSBA titres > 4 against MenB target strains (per visit) hSBA GMTs (with 95% CI) against MenB target strains	n=38 Healthy adults, aged 23-55, public health laboratory workers were enrolled and received vaccination in the first visit, seven withdrew from the study 4CMenB was given at 0, 3, 6 month time points. Blood samples taken in the same visits and at 2,7 month time points (total 5 visits)	**Seroprotection** Proportions of subjects with hSBA titres > 4 against MenB target strains prior to immunization, 3 months after dose 1, 3 months after dose 2, 1 month after dose 3 44/76-SL *Prior to Dose 1: (*33/38 (87 %) *Dose 1*: 32/32 (100 %) *Dose 2*: 32/32(100 %) Dose3: 28/28(100%) NZ 98/254 *Prior to Dose 1*:27/38 (71 %) *Dose 1*: 32/32 (100 %) *Dose 2*: 31/32 (97 %) Dose 3:30/30 (100%)	Level II-1 N/A (poster)

Evidence related to immunogenicity of 4CMenB vaccine initiated in adults aged 18 to 55 years

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
			Menveo® was administered concomitantly at 0 months.	5/99 *Prior to Dose 1*: 27/38 (71 %) *Dose 1*:32/32 (100 %) *Dose 2*:32/32 (100 %) Dose 3:30/30 (100%) **hSBA GMTs (with 95% CI) against MenB target strains (extrapolated from figures)** 44/76-SL *Prior to Dose 1*:16(95% CI: 10, 30) *Dose 1*: 192 (95% CI: 116, 348) *Dose 2*: 120 (95% CI: 64, 245) Dose 3:260 (95% CI: 192, 384) NZ 98/254 *Prior to Dose 1*: 8(95% CI: 5, 16) *Dose 1*: 256 (95% CI: 128, 518) *Dose 2*: 128 (95% CI: 64, 265) Dose 3:256 (95% CI: 130, 512) 5/99 *Prior to Dose 1*: 8 (95% CI: 14, 16) *Dose 1*: 348 (95% CI: 614, 1220) *Dose 2*: 192 (95% CI: 85, 384) Dose 3:896 (95% CI: 512, 1536)	

Table 5: Summary of evidence related to safety of 4CMenB vaccine

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Findlow J, Borrow R, Snape MD, Dawson T, Holl, A, et al. Multicenter, open-label, randomized phase II controlled trial of an investigational recombinant Meningococcal serogroup B vaccine with and without outer membrane vesicles, administered in infancy. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2010 11;51(10):1127-1137.	4CMenB 0.5 mL Intramuscular (IM), thigh Other infant vaccines: DPTPHib (Pediacel®; Sanofi Pasteur) at 2, 3, 4 months of age; pneumococcal conjugate vaccine (Prevenar®, Wyeth Pharmaceuticals) at 2, 4, 13 months of age; MenC conjugate vaccine (Menjugate®; Novartis) at 3, 5 months of age; MenC-Hib conjugate vaccine (Menitorix®; GSK) at 12 months of age; and MMR (Priorix™; GSK)	Phase II RCT Parallel assignment Open label Multicenter UK NCT00381615 Endpoints: Local and systemic reactions, axillary temperature, any medication use, any medical attention and other adverse events recorded daily for 7 days after each vaccination; additional data on adverse events recorded until 18 months of age	N=147 enrolled; n=46 received 4CMenB vaccine according to infant schedule Healthy 2 month old infants 4CMenB vaccine given at 2, 4, 6 and 12 months of age with other infant vaccines (n=46 infants, mean age 61.0 days, 54% male)	**Local reactogenicity**, % of subjects: Tenderness (severe defined as child cried when injected limb moved) 36.3% any, 8.1% severe (all doses*) 48.5% any, 10.5% severe (fourth dose) Erythema (severe ≥50 mm diameter) 91.4% any, 0% severe (all doses*) 96% any, 0% severe (fourth dose) Induration (severe ≥50 mm diameter) 53.6% any, 0% severe (all doses*) 70.5% any, 0% severe (fourth dose) **Systemic reactogenicity**, % of subjects: Change in eating habits 25.5% (all doses*) Sleepiness 22.9% (all doses*) 64% (first dose) Vomiting 8.0% (all doses*) Diarrhea 9.5% (all doses*) Irritability 68.3% (all doses*) Unusual crying 16.0% (all doses*) Rash 11.4% (all doses*) Fever ≥38°C	Level I, Fair

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
	at 13 months of age			9.2% (all doses*) 18% (first dose) *calculated by review authors **Serious adverse events**: None attributed to 4CMenB or routine vaccines, as judged by investigators	
Snape MD, Dawson T, Oster P, Evans A, John TM, Ohene-Kena B, et al. Immunogenicity of two investigational serogroup B meningococcal vaccines in the first year of life: a randomized comparative trial. Pediatr Infect Dis J 2010 11;29(11):e71-e79.	4CMenB 0.5 mL IM, thigh Other infant vaccines: MCCV-Hib (Menitorix®; GSK) at 12 months of age in opposite thigh to study vaccine	Phase II RCT Parallel assignment Single-blind (parent/guardian) Single center UK NCT00433914 Endpoints: Safety and tolerability of 4CMenB vaccine (entire study period): axillary temperature and local and systemic reactions 7 days after each vaccination, use of analgesic and antipyretic medicine, and	N=60 enrolled; n=30 received 4CMenB vaccine Healthy 6-8 month old infants 4CMenB at 6-8 months of age, 60 days later and 12 months of age with routine vaccines; n=30 (mean age 7.1 months; 40.0% male)	**Local reactogenicity**, % of subjects, all doses combined*: Tenderness (severe reaction defined as pain on movement of leg) 35.3% any, 4.7% severe Erythema (severe reaction defined as >100 mm in diameter) 90.6% any, 1.2% severe Induration (severe reaction defined as >100 mm in diameter) 61.2% any, 0% severe **Systemic reactogenicity**, % of subjects, all doses combined*: Change in eating habits: 23.5% Sleepiness: 27.1% Vomiting: 10.6% Diarrhea: 12.9% Irritability: 57.6% Unusual crying: 14.1% Rash: 12.9% Fever >38°C (axillary temperature) 8.2% (all doses*) 10.0% (dose one) *Calculated by review authors	Level I, Fair

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
		adverse events requiring a physician visit measured within 30 days of study vaccine administration and 6 months after the final study vaccine. Vaccine safety data were reported descriptively and included those that received at least 1 dose of vaccine.		**Serious adverse events**: • Fever (n=1): defined as axillary temperature >39.5°C, following the third dose of 4CMenB. • Febrile convulsion associated with tonsillitis (n=1): occurred 5 days after the third dose of 4CMenB, unrelated to study vaccine as per study investigators.	
Prymula R, Esposito S, Kittel C, Kohl I, Toneatto D, Dull P. Prophylactic paracetamol in infants decreases fever following concomitant administration of an investigational meningococcal serogroup B vaccine with routine immunizations. Poster session presented at: 29th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); 2011 June 7-11; The Hague,	4CMenB Other infant vaccines: DTaP-IPV-HBV/Hib (Infanrix-hexa®, GSK) and heptavalent pneumococcal vaccine (Prevenar®, Wyeth Pharmaceuticals) Paracetamol:	Phase II RCT Parallel assignment Masking unclear Multicenter Argentina, Chile, Czech Republic, Hungary, Italy NCT00937521 Endpoints: Rectal	N enrolled unclear; n=367 received 4CMenB vaccine Healthy 2 month old infants 4CMenB vaccine given at 2, 3 and 4 months of age with concomitant infant vaccines (n=184 infants) 4CMenB vaccine given at 2, 3 and 4 months of age with	**Systemic reactogenicity**, % of subjects, all doses combined*: Fever (temperature ≥38.5°C) *Without paracetamol*: 43.3% (all doses) 51% (first dose) *With paracetamol*: 18.3% (all doses) 25% (first dose) Fever (temperature ≥39.5°C) *Without paracetamol*: 4.0% (all doses) 5% (first dose) *With paracetamol*: 1.0% (all doses)	Level I, N/A (poster)

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Netherlands. Data on file with Novartis	10-15 mg/kg per dose	temperature measured for 7 days post-vaccination.	concomitant infant vaccines and three doses of prophylactic paracetamol (one dose before vaccination and two doses separated by 4-6 hours after vaccination) (n=183 infants)	1% (first dose) *calculated by review authors	
Gossger N, Snape MD, Yu LM, Finn A, Bona G, Esposito S, et al. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. JAMA 2012 Feb 8;307(6):573-582.	4CMenB 0.5 mL IM, thigh Other infant vaccines: DTap-HBV-IPV/Hib (Infanrix-hexa®; GSK) and 7-valent pneumococcal glycoconjugate vaccine (Prevenar®, Wyeth Pharmaceuticals) 0.5 mL IM, opposite thigh to study vaccine	Phase IIB RCT Parallel assignment Open label Multicenter Belgium, Czech Republic, Germany, Italy, Spain, UK NCT00721396 Endpoints: Safety and tolerability of three doses of 4CMenB given: concomitantly with routine vaccines (2, 4, 6 months of age, or 2, 3, 4	N=1,885 enrolled; n=1,571 received 4CMenB Healthy 2 month old infants *Concomitant* group: 4CMenB vaccine given at 2, 4 and 6 months of age with concomitant infant vaccines (n=622 infants, of which n=602-624 in analysis) *Separate* group: 4CMenB vaccine given at 2, 4 and 6 months of age with other infant vaccines given at 3,	**Local reactogenicity**, % of subjects, all doses combined*: Pain (severe defined as child cried when injected limb moved or did not move injected limb) *Concomitant*: 60.9% any, 14.2% severe *Separate*: 55.0% any, 9.4% severe *Accelerated*: 61.8% any, 13.8% severe *Routine*: 34.5% any, 1.8% severe Erythema (severe >100 mm diameter) *Concomitant*: 66.0% any, 0% severe *Separate*: 66.6% any, 0% severe *Accelerated*: 67.2% any, 0% severe *Routine*: 51.8% any, 10% severe (all doses) 51% any, 30% severe (dose three) Induration (severe >100 mm diameter) *Concomitant*: 49.6% any, 0% severe *Separate*: 51.9% any, 0% severe *Accelerated*: 51.8% any, 0% severe *Routine*: 33.4% any, 0% severe Swelling (severe >100 mm diameter)	Level I, Fair

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
		months of age), or alone (2, 4, 6 months of age); specifically, solicited local and systemic reactions, axillary temperature and adverse events daily for 7 days after each vaccination, with safety follow-up completed 6 months after last dose of 4CMenB or at age 10 months in control group All subjects who received at least one dose of vaccine and provided post-baseline safety data were included in analysis	5 and 7 months of age (n=632 infants, of which n=601-626 in analysis) *Accelerated* group: 4CMenB vaccine given at 2, 3 and 4 months of age with concomitant infant vaccines (n=317 infants, of which n=310-317 in analysis) *Routine* group: Routine vaccines given alone at 2, 3 and 4 months of age (n=314 infants, of which n=304-311 in analysis)	*Concomitant*: 28.0% any, 0% severe *Separate*: 29.4% any, 0.05% severe *Accelerated*: 28.9% any, 0% severe *Routine*: 24.8% any, 0% severe **Systemic reactogenicity**, % of subjects, all doses combined*: Change in eating habits (severe defined as more than two missed feedings) *Concomitant*: 51.3% any, 4.0% severe *Separate*: 37.8% any, 2.2% severe *Accelerated*: 52.9% any, 3.9% severe *Routine*: 29.1% any, 1.7% severe Sleepiness (severe defined as sleeping most of the time and hard to arouse) *Concomitant*: 62.0% any, 3.4% severe *Separate*: 48.9% any, 2.5% severe *Accelerated*: 66.1% any, 3.4% severe *Routine*: 48.7% any, 1.8% severe Vomiting (severe defined as several vomiting episodes and cannot keep food down for prolonged time) *Concomitant*: 15.9% any, 0.9% severe *Separate*: 11.0% any, 0.3% severe *Accelerated*: 15.1% any, 0.4% severe *Routine*: 12.8% any, 0.2% severe Diarrhea (severe defined as more than 6 liquid stools with no solid consistency) *Concomitant*: 22.3% any, 1.3% severe *Separate*: 17.8% any, 0.7% severe *Accelerated*: 22.5% any, 0.6% severe	

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				Routine: 20.1% any, 0.9% severe Irritability (severe defined as unable to be consoled) *Concomitant*: 72.8% any, 9.7% severe *Separate*: 59.1% any, 5.7% severe *Accelerated*: 73.5% any, 7.9% severe *Routine*: 51.6% any, 3.6% severe Unusual crying (severe defined as unusual, high-pitched screaming, unlike child's normal crying, that persists for ≥3 hours) *Concomitant*: 63.3% any, 7.8% severe *Separate*: 48.3% any, 4.0% severe *Accelerated*: 64.7% any, 6.5% severe *Routine*: 37.0% any, 3.3% severe Rash (severe defined as urticarial rash) *Concomitant*: 5.4% any; 0.7% severe *Separate*: 5.0% any; 1.4% severe *Accelerated*: 5.0% any; 0.6% severe *Routine*: 4.6% any; 1.5% severe Fever ≥38°C *Concomitant*: 57.8% (all doses*); 61% (dose one) *Separate*: 35.0% (all doses*); 38% (dose one) *Accelerated*: 53.4% (all doses*); 58% (dose one) *Routine*: 29.8% (all doses*); 31% (dose one) Fever ≥39°C *Concomitant*: 12.0% (all doses*); 12% (dose one)	

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				Separate: 6.0% (all doses*); 7% (dose one) *Accelerated*: 9.5% (all doses*); 11% (dose one) *Routine*: 3.3% (all doses*); 4% (dose one) *calculated by review authors **Serious adverse events**: • Medically attended fever (n=6): for all cases onset was within 2 days of 4CMenB, possibly related to study vaccine. • Seizure (n=3): 2 cases following routine vaccination in *separate* group and *accelerated* group, possibly related to routine vaccination; 1 case following 4CMenB vaccination in *separate* group, possibly related to 4CMenB vaccine. • Febrile seizure (n=1): onset 2 days after 2nd dose of 4CMenB in *separate* group, possibly related to 4CMenB vaccine. • Hypotonic hyporesponsive episode (n=2): 1 case with onset within 12 hours of concomitant 4CMenB vaccine and routine vaccines, possibly related to 4CMenB; 1 case with onset within 6 hours of routine vaccines in *separate* group, possibly related to routine vaccines. • Kawasaki disease (n=2): 1 case was considered possibly related to 4CMenB by an independent expert panel. • Aseptic meningitis (n=1): following concomitant	

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				vaccination, possibly related to study or routine vaccines. • Retinal dystrophy (believed to be congenital) (n=1): following concomitant vaccination, possibly related to study or routine vaccines. • Transient synovitis of right hip (n=1): following concomitant vaccination, possibly related to study or routine vaccines. • Transient hearing loss (noted by a parent) (n=1): following concomitant vaccination, possibly related to study or routine vaccines. • Transient apnea (n=1): following concomitant vaccination, possibly related to study or routine vaccines. Study withdrawal due to SAE (per group of modified ITT population): n=4 in *concomitant* group, n=7 in *separate* group, n=2 in *accelerated* group and none in *routine* group	
Esposito S, Vesikari T, Kimura A, Ypma E, Toneatto D, Dull PM. Tolerability of a three-dose schedule of an investigational, multicomponent, meningococcal serogroup B vaccine and routine infant vaccines in a lot consistency trial. Poster session presented at: 17th International Pathogenic Neisseria Conference (IPNC); 2010 Sept 11-16;	4CMenB Other infant vaccines: DTaP-IPV-HBV/Hib (Infanrix-hexa®, GSK) and 7-valent pneumococcal conjugate vaccine (Prevenar®, Pfizer)	Phase III RCT Parallel assignment Open label and observer-blind cohorts Multicenter Austria, Czech Republic, Finland, Germany, Italy NCT00657709	N=3,630 enrolled; n=2,459received 4CMenB vaccine in cohorts with safety measured Healthy 2 month old infants 4CMenB-Lot 1 given at 2, 4 and 6 months of age with concomitant infant vaccines (n=600,	**Local reactogenicity**, % of subjects in observer-blind cohort, all doses combined (severe not defined): Tenderness *4CMenB*: 86% any, 14% severe *Menjugate*: 55% any, 3.5% severe Erythema *4CMenB*: 77.75% any, 0% severe *Menjugate*: 55% any, 0% severe Induration *4CMenB*: 77.75% any, 0% severe *Menjugate*: 47% any, 0% severe Swelling *4CMenB*: 36% any, 0% severe *Menjugate*: 19% any, 0% severe	Level I, Good

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Banff, AB, Canada. Data on file with Novartis Vesikari T, Esposito S, Prymula R, Ypma E, Kohl I, Toneatto D, Dull P, Kimura A, for the EU Meningococcal B Infant Vaccine Study Group. immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccines: results of two randomised trials. The Lancet. Published online January 14th, 2013.		Endpoints: Solicited local and systemic reactions and medically attended fever for days 1-7 following vaccination; adverse events were evaluated throughout the study; and infants were followed up to 12 months of age All subjects receiving at least 1 injection and providing post-baseline safety data were included in the safety and tolerability analysis	open label cohort; n=200, observer-blind cohort) 4CMenB-Lot 2 given at 2, 4 and 6 months of age with concomitant infant vaccines (n=600, open label cohort; n=200, observer-blind cohort) 4CMenB-Lot 3 given at 2, 4 and 6 months of age with concomitant infant vaccines (n=600, open label cohort; n=200, observer-blind cohort) Routine vaccines only given at 2, 4 and 6 months of age (n=600, open label cohort) Menjugate™ vaccine given at 2, 4 and 6 months of age with infant vaccines (n= 600, observer-blind	**Systemic reactogenicity**, % of subjects in observer-blind cohort, all doses combined (severe reaction not defined): Changed eating habits *4CMenB*: 75% any, 5% severe *Menjugate*: 53.5% any, 1.5% severe Sleepiness *4CMenB*: 87.75% any, 5% severe *Menjugate*: 75% any, 5% severe Vomiting *4CMenB*: 27.5% any, 2% severe *Menjugate*: 23% any, 2% severe Diarrhea *4CMenB*: 42.25% any, 2% severe *Menjugate*: 34.5% any, 2% severe Irritability *4CMenB*: 90% any, 7.25% severe *Menjugate*: 78.5% any, 4.5% severe Unusual crying *4CMenB*: 91% any, 7.75% severe *Menjugate*: 75% any, 5% severe Rash *4CMenB*: 10% any, 2% severe *Menjugate*: 9.25% any, 1% severe Fever, % of subjects in observer-blind and open label cohorts combined: Temperature 38.5°C to <39°C *4CMenB all doses combined**: 0.0% (30 min.); 22.6% (6 hours); 15.6% (day 2); 1.5% (day 3); 0.7% (day 4) *4CMenB dose 1*:	

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
			cohort)	0% (30 min.); 24.75% (6 hours); 11% (day 2); 0% (day 3); 0% (day 4) *4CMenB dose 2*: 0% (30 min.); 24% (6 hours); 20% (day 2); 2% (day 3); 1% (day 4) Temperature 39°C to <39.5°C *4CMenB all doses combined**: 0.0% (30 min.); 10.5% (6 hours); 4.5% (day 2); 0.3% (day 3); 0.2% (day 4) *4CMenB dose 1*: 0% (30 min.); 12% (6 hours); 2.5% (day 2); 0% (day 3); 0% (day 4) Temperature 39.5°C to <45°C *4CMenB all doses combined**: 0.0% (30 min.); 3.8% (6 hours); 1.0% (day 2); 0.0% (day 3); 0.0% (day 4) *4CMenB dose 1*: 0% (30 min.); 4% (6 hours); 1% (day 2); 0% (day 3); 0% (day 4) Temperature ≥45°C *4CMenB all doses combined**: 0.0% (30 min.); 0.3% (6 hours); 0.0% (day 2); 0.0% (day 3); 0.0% (day 4) Medically attended fever, parent of subjects in open label cohort were informed of possibility of fever by study investigators: *4CMenB (open label cohort)*: 0.5% (all doses combined*) 1.42% (any dose)	

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				Routine (open label cohort): 0.7% (all doses combined*) 1.82% (any dose) *4CMenB (observer-blind subset)*: 1.9% (all doses combined*) 5.27% (any dose) *Menjugate (observer-blind subset)*: 0.9% (all doses combined*) 1.99% (third dose) 2.77% (any dose) *calculated by review authors **Serious adverse events**: Serious adverse events reported include: pyrexia, cerebral palsy, microcephaly, irritability, diarrhea and upper respiratory tract infection, vaccine reaction (fever, diarrhea, loss of appetite, swelling at injection site), arthritis, convulsion with fever, varicella, tremor, seizure (analysis and interpretation of data is ongoing). <1% of subjects discontinued the study due to an adverse event	
Vesikari T, Prymula R, Liese J, Kollaritsch H, Bona G, Kimura A, et al. Booster dose at 12 months of an investigational meningococcal serogroup B vaccine (4CMenB) in healthy toddlers previously primed at 2, 4, 6 months. Poster session presented	4CMenB 0.5 mL MMRV (Priorix-Tetra®, GSK)	Phase III RCT (extension study) Parallel assignment Open label Multicenter Austria, Czech	N enrolled unclear; n=1,555 received 4CMenB vaccine Healthy 12 month old children who previously received 4CMenB vaccine at 2, 4 and 6 months of age with routine	**Local reactogenicity**, % of subjects following booster dose: Tenderness (severe reaction defined as child cried when injected limb moved) 70% any; 13.5% severe (concomitant) 70% any; 14.5% severe (separate) Erythema (severe reaction not defined) 65.5% any; 7% severe (concomitant)	Level I, Good

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
at: 29th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); 2011 Jun 7-11; The Hague, Netherlands. Data on file with Novartis Vesikari T, Esposito S, Prymula R, Ypma E, Kohl I, Toneatto D, Dull P, Kimura A, for the EU Meningococcal B Infant Vaccine Study Group. immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccines: results of two randomised trials. The Lancet. Published online January 14th, 2013.		Republic, Finland, Germany, Italy NCT00847145 Endpoints: Solicited local and systemic reactions for 7 days after each vaccination, other adverse events recorded for 28 days; temperature monitored daily for 28 days in concomitant group and 7 days in separate group.	vaccines *Concomitant* group: 4CMenB vaccine (booster) given at 12 months of age with concomitant MMRV vaccine (n=766 children, age 12.3 mo., 0.5 SD, 52% male) *Separate* group: 4CMenB vaccine (booster) given at 12 months of age with MMRV vaccine given at 13 months of age (n=789 children, age 12.3 mo., 0.5 SD, 48% male)	67% any; 8% severe (separate) Induration (severe reaction not defined) 50% any; 5% severe (concomitant) 54.5% any; 4% severe (separate) Swelling (severe reaction not defined) 36% any; 7% severe (concomitant) 35% any; 6% severe (separate) **Systemic reactogenicity**, % of subjects following booster dose (severe reaction not defined): Change in eating habits 40.5% any; 2.5% severe (concomitant) 39.5% any; 2.5% severe (separate) Sleepiness 46.5% any; 1.5% severe (concomitant) 44.5% any; 1.2% severe (separate) Vomiting 7.5% any; 1% severe (concomitant) 5.5% any; 1% severe (separate) Diarrhea 25.5% any; 1.5% severe (concomitant) 20% any; 1.5% severe (separate) Irritability 72.5% any; 5% severe (concomitant) 68% any; 3.4% severe (separate) Unsual crying 43.5% any; 2.5% severe (concomitant) 37.5% any; 2.5% severe (separate) Rash 7.5% any; 4% severe (concomitant) 7.5% any; 2.5% severe (separate)	

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				Fever [‡] 48%; 1.5% severe (concomitant) 40%; 0% severe (separate) **Serious adverse events**: • Febrile convulsion (n=1): occurred in concomitant group 9 days after MMRV and 4CMenB, possibly related to vaccination. • Pyrexia (n=1): occurred in concomitant group, possibly related to vaccination	
Saroey P, Snape MD, John TM, Robinson H, Kelly S, Gossger N, Wang H, Toneatto D, Dull PM, Kimura A, Pollard AJ Persistence of bacterial antibody following early infant immunization with serogroup B meningococcal vaccine and immunogenicity of pre-school booster doses- A follow on study. European Society for Paediatric Infectious Diseases (ESPID); 2012, 08-12 May, Thessaloniki, Greece Martin NG , Snape MD, Robinson H, John T, Kelly S, Toneatto D, Dull P, Pollard AJ.	4CMenB 0.5 mL IM, thigh	Follow-on phase 2, open labelled, single centre randomised study UK NCT01027351 **Endpoints** Local reactogenicity Severe erythema, induration or swelling were defined as a reaction size > 50mm. Systemic Reactogenicity. Fever is defined as temperature ≥38°C and graded	113 participants were recruited for follow-on study, of whom 70 were from the original study and 43 were Men B vaccine naïve for comparison (results presented in safety of 4CMenB vaccine in 2-10 year olds section) Group 4CMenB-2,4,6-12) received 4 doses of 4CMenB vaccine at 2,4,6 and 12 months in early infant study n=19 For this study, they were given a	**Group 4CMenB-2,4,6,12)** **Local reactogenicity,** % of subjects (after 4th dose) Pain (severe defined as inability to perform daily activity) 74% (severe 11%) Erythema (severe defined as > 50mm) 100% Induration (severe defined as > 50mm) 46% (severe 5%) Swelling (severe defined as > 50mm) 25% (severe 7%) **Systemic reactogenicity,** % of subjects (after 4th dose), severe signs and symptoms not defined Change in eating habits: 53% Sleepiness: 62% Vomiting: 15% Diarrhea: 5% Irritability: 52 (severe 4%) Headache: 0% Arthralgia: 33% (severe 4%) Rash: 0% Fever ≥38°: 5%	Level I NA (poster)

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Reactogenicity and safety of investigational serogroup B meningococcal vaccines given at 40 months of age to primed and vaccine naïve children. European Society for Paediatric Infectious Diseases (ESPID); 2012, 08-12 May, Thessaloniki, Greece		as severe when ≥ 40°C. Fever in the second poster was defined as >38 and>39	booster dose at 40 months (Group 4CMenB-12) Received 1 dose of 4CMenB vaccine at 12 months in early infant study. For this study, they were given 2 booster at 40 and 42 months of age n=8	Group 4CMenB-12 **Local reactogenicity,** % of subjects, dose 2, dose 3 Pain (severe defined as inability to perform daily activity) 100% (severe 12%), 90% (severe 24%) Erythema (severe defined as > 50mm) 100%, 100% Induration (severe defined as > 50mm) 63%, 75% Swelling (severe defined as > 50mm) 25% , 50% **Systemic reactogenicity,** % of subjects, dose 2, dose 3 Change in eating habits: 25%, 25% Sleepiness: 50%, 38% Vomiting: 0%, 0% Diarrhea: 0%, 12% Irritability: 63%, 63% Headache: 0%, 15% Arthralgia: 24%, 25% (severe [not clearly defined] 12%) Rash: 13%, 0% Fever ≥38°C: 0%, 0% **Serious adverse events:** None in these groups	
Philip J, Snape MD, Robinson H, Kelly S, Pollard AJ, John TM, Gossger N, Toneatto D, Kittel C, Kimura A, Dull PM. Bacterial antibody persistence two years	4CMenB 0.5 mL IM, thigh Recombinant-proteins alone (rMenB)	Phase II RCT Parallel assignment Single-blind (parent/guardian)	4CMenB group received 4CMenB at 6, 8 and 12 months in the original study. This is an extension of the original study:	**Local reactogencity,** % of subjects Pain (severe defined as inability to move limb) 100% (severe 15%) Erythema: 100% Induration: 35% Swelling: 44%	Level I NA (poster)

Evidence related to safety of 4CMenB vaccine initiated in infants aged ≤ 12 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
following meningococcal B vaccination at 6,8,12 months in 40 month old children. European Society for Paediatric Infectious Diseases (ESPID); 2012, 08-12 May, Thessaloniki, Greece Martin NG, Snape MD, Robinson H, John T, Kelly S, Toneatto D, Dull P, Pollard AJ. Reactogenicity and safety of investigational serogroup B meningococcal vaccines given at 40 months of age to primed and vaccine naïve children European Society for Paediatric Infectious Diseases (ESPID); 2012, 08-12 May, Thessaloniki, Greece		Single center UK NCT01026974 Endpoints: systemic and local reactions Fever is defined as temperature ≥38C and graded as severe when ≥ 40 C. Pain is severe if occurring on movement of leg, and erythema, induration and swelling severe if greater than 50 mm.	4CMenB group n=14 enrolled and received 4CMenB at 40 months of age. Blood samples were taken at enrolment (40 month) and 41 month (one month post first booster).	**Systemic reactogencity,** % of subjects Change in eating habits: 35% Sleepiness: 50% (severe 3%) Vomiting: 21% Diarrhea: 7% Irritability: 80% Headache: 7% Fever > 38° C: 7% (all > 39° C) **Serious adverse events** None in this group	

Evidence related to safety of 4CMenB vaccine initiated in children aged 12 to 24 months

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Findlow J, Borrow R, Snape MD, Dawson T, Holl, A, et al. Multicenter, open-label, randomized phase II controlled trial of an investigational recombinant Meningococcal serogroup B vaccine with and without outer membrane vesicles, administered in infancy. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2010 11;51(10):1127-1137.	4CMenB 0.5 mL IM, thigh Other infant vaccines: DPTPHib (Pediacel®; Sanofi Pasteur) at 2, 3, 4 months of age; pneumococcal conjugate vaccine (Prevenar®, Wyeth Pharmaceuticals) at 2, 4, 13 months of age; MenC conjugate vaccine (Menjugate®; Novartis) at 3, 5 months of age; MenC-Hib conjugate vaccine (Menitorix®; GSK) at 12 months of age; and MMR (Priorix™; GSK) at 13 months of age	Phase II RCT Parallel assignment Open label Multicenter UK NCT00381615 Endpoints: Axillary temperature, medication, local reactions, systemic reactions and medical attention recorded 7 days after each dose; as well as additional data on adverse events until day 481 (18 months of age)	n=147 enrolled; n=23 children received 4CMenB vaccine Healthy 12 month old children 4CMenB vaccine given at 12 months of age with other infant vaccines (n=23 children, mean age 60.7 days, 55 to 79 days, 74% male)	**Local reactogenicity**, % of subjects, following single 12-month dose: Tenderness (severe defined as child cried when injected limb moved) 30% any, 13.5% severe Erythema (severe ≥50 mm diameter) 100% any, 4% severe Induration (severe ≥50 mm diameter) 83% any, 0% severe **Systemic reactogenicity**, % of subjects, following single 12-month dose: Change in eating habits: 26.5% Sleepiness: 43% Vomiting: 13.5% Diarrhea: 4.5% Irritability: 57% Unusual crying: 17% Rash: 4% Fever (axillary temperature ≥38°C) : 17% **Serious adverse events**: None attributed to 4CMenB or routine vaccines, as judged by investigators	Level I, Fair

Evidence related to safety of 4CMenB vaccine initiated in children aged 12 to 24 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Prymula R, Vesikari T, Esposito S, Kohl I, Ypma E, Kleinschmidt A, et al. Catch-up vaccination of healthy toddlers with an investigational multicomponent meningococcal serogroup B vaccine (4CMenB) – exploration of a two-dose schedule. Poster session presented at: 29th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); 2011 Jun 7-11; The Hague, Netherlands. [‡] Data on file with Novartis	4CMenB 0.5 mL MMRV (Priorix-Tetra®, GSK)	Phase III RCT (extension study) Parallel assignment Open label Multicenter Austria, Czech Republic, Finland, Germany, Italy NCT00847145 Endpoints: Solicited local and systemic reactions and other adverse events for 7 days after each vaccination, medically attended serious adverse events throughout study duration. All subjects were included in the safety analysis except for one subject (received 4CMenB vaccine at 13 and 15	N enrolled unclear; n=402 received 4CMenB vaccine Healthy 12 month old children 4CMenB vaccine given at 12 and 14 months of age (dose 1 and 2) with MMRV vaccine given at 12 months of age (n=117 children, age 12.3 months, 0.5 SD, 53% male) 4CMenB vaccine given at 13 and 15 months of age (dose 1 and 2) with MMRV vaccine given at 12 months of age (n=285 children, age 12.3 months, 0.5 SD, 54% male)	**Local reactogenicity**, % of subjects, following first and second dose: Tenderness (severe reaction defined as child cried when injected limb moved) *4CMenB (12, 14 mo. of age)* 57% any; 10% severe (first dose) 67% any; 18.5% severe (second dose) *4CMenB (13, 15 mo. of age)* 56% any; 10% severe (first dose) 66% any; 16% severe (second dose) Erythema (severe reaction not defined) *4CMenB (12, 14 mo. of age)* 70% any; 2% severe (first dose) 60% any; 2.5% severe (second dose) *4CMenB (13, 15 mo. of age)* 62.25% any; 1% severe (first dose) 57.5% any; 3.5% severe (second dose) Induration (severe reaction not defined) *4CMenB (12, 14 mo. of age)* 52% any; 1% severe (first dose) 48% any; 1% severe (second dose) *4CMenB (13, 15 mo. of age)* 40% any; 1% severe (first dose) 42% any; 1% severe (second dose) Swelling (severe reaction not defined) *4CMenB (12, 14 mo. of age)* 31% any; 1% severe (first dose) 29% any; 1% severe (second dose)	Level I, N/A (poster)

Evidence related to safety of 4CMenB vaccine initiated in children aged 12 to 24 months					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
		months of age with MMRV vaccine given at 12 months of age) who was withdrawn after receiving their first MMRV vaccination. Temperature was analyzed for days 1-4 after each 4CMenB vaccine, and days 5-28 after each MMRV vaccine.		*4CMenB (13, 15 mo. of age)* 29% any; 1% severe (first dose) 31% any; 3% severe (second dose) **Systemic reactogenicity**, % of subjects, following first and second dose (severe reaction not defined): Change in eating habits *4CMenB (12, 14 mo. of age)* 38% any; 0% severe (first dose) 34.5% any; 3% severe (second dose) *4CMenB (13, 15 mo. of age)* 34.5% any; 1% severe (first dose) 31% any; 2% severe (second dose) Sleepiness *4CMenB (12, 14 mo. of age)* 47% any; 1% severe (first dose) 40.5% any; 0% severe (second dose) *4CMenB (13, 15 mo. of age)* 39% any; 1% severe (first dose) 38.5% any; 1% severe (second dose) Vomiting *4CMenB (12, 14 mo. of age)* 2% any; 0% severe (first dose) 3% any; 1% severe (second dose) *4CMenB (13, 15 mo. of age)* 5% any; 1% severe (first dose) 3% any; 0% severe (second dose) Diarrhea *4CMenB (12, 14 mo. of age)* 29% any; 0% severe (first dose) 20.5% any; 0% severe (second dose)	

Evidence related to safety of 4CMenB vaccine initiated in children aged 12 to 24 months

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				4CMenB (13, 15 mo. of age) 15.5% any; 0% severe (first dose) 14.5% any; 0% severe (second dose) Irritability *4CMenB (12, 14 mo. of age)* 70% any; 3% severe (first dose) 62.5% any; 3% severe (second dose) *4CMenB (13, 15 mo. of age)* 60% any; 2% severe (first dose) 56.5% any; 3% severe (second dose) Unusual crying *4CMenB (12, 14 mo. of age)* 37% any; 2% severe (first dose) 35.5% any; 3% severe (second dose) *4CMenB (13, 15 mo. of age)* 28% any; 1% severe (first dose) 26% any; 1% severe (second dose) Rash *4CMenB (12, 14 mo. of age)* 8% any; 1% severe (first dose) 5% any; 2% severe (second dose) *4CMenB (13, 15 mo. of age)* 5% any; 2% severe (first dose) 4% any; 1% severe (second dose) Fever *4CMenB (12, 14 mo. of age)* ‡ 43%, 0% severe (dose unclear) *4CMenB (13, 15 mo. of age)* ‡ 35%, 0% severe (dose unclear)	

Evidence related to safety of 4CMenB vaccine initiated in children aged 12 to 24 months

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				Fever (temperature ≥38 C) *4CMenB (12, 14) + MMRV (12 mo. of age)* 37% (dose 1, 1-4 days) 44% (dose 1, 5-28 days) 40% (dose 2, 1-4 days) *4CMenB (13, 15) + MMRV (12 mo. of age)* 35.5% (dose 1, 1-4 days) 34.5% (dose 2, 1-4 days) 8% (MMRV, 1-4 days) 53% (MMRV, 5-28 days) **Serious adverse events** No subjects withdrew due to vaccine-related serious adverse events; one subject withdrew after the first dose of 4CMenB vaccine (at 13 months of age) with a diagnosis of asthma.	

Evidence related to safety of 4CMenB vaccine initiated in children aged 2 to 10 years

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Saroey P, Snape MD, John TM, Robinson H, Kelly S, Gossger N, Wang H, Toneatto D, Dull PM, Kimura A, Pollard AJ. Persistence of bacterial antibody following early infant immunization with serogroup B meningococcal vaccine and immunogenicity of pre-school booster doses- A follow on study European Society for Paediatric Infectious Diseases (ESPID); 2012, 08-12 May, Thessaloniki, Greece Martin NG , Snape MD, Robinson H, John T, Kelly S, Toneatto D, Dull P, Pollard AJ. Reactogenicity and safety of investigational serogroup B meningococcal vaccines given at 40 months of age to primed and vaccine naïve children. European Society for Paediatric Infectious Diseases (ESPID); 2012,	4CMenB 0.5 mL IM, thigh Recombinant-proteins alone (rMenB)	Follow-on phase 2, open labelled, single centre randomised study UK NCT01027351 **Endpoints** Local and systemic reactions recorded daily for seven days after vaccination. Local reactogenicity: Severe pain defined as inability to move limb. Severe erythema, induration or swelling were defined as a reaction size > 50mm. Systemic Reactogenicity. Fever is defined as temperature ≥38°C and graded	113 participants were recruited for follow-on study, of whom 70 were from the original study and 43 were Men B vaccine naïve for comparison ("Control") "Control" group n=43 received 2 doses of 4CMenB vaccine at 40 and 42 months in early infant study For this study, they received 2 doses of 4CMenB vaccine at 40 and 42 months	**Local reactogenicity**, % of subjects dose 1, dose 2 Pain (severe defined as inability to move limb) 92% (severe 20%), 85% (severe 15%) Erythema (severe defined as > 50mm) 98% (severe 2%), 90 % (severe 6%) Induration (severe defined as > 50 mm) 32%, 50% Swelling (severe defined as > 50 mm) 48%(severe 2%), 63% **Systemic reactogenicity,** % of subjects dose 1, dose 2 (severe signs and symptoms not defined) Change in eating habits:36%(2% severe), 38% Sleepiness:38%,37% Vomiting:2%,0% Diarrhea:13%,2% Irritability: 75% (severe 6%), 58% (severe 3%) Headache: 15%, 15% (severe 2%) Arthralgia: 31% (severe 8%), 21% (severe 6%) Rash: 2%, 5% Fever >38°C: 10%, 12% Fever >39°C: 0% ,4% Fever>40°C: 0%, 2%	Level I NA (poster)

Evidence related to safety of 4CMenB vaccine initiated in children aged 2 to 10 years

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
08-12 May, Thessaloniki, Greece		as severe when ≥ 40°C. Fever in the Martin poster was defined as >38°C and > 39°C		**Serious adverse events** One case of cervical lymphadenitis considered by the others to be unrelated to 4CMenB vaccine	
Philip J, Snape MD, Robinson H, Kelly S, Pollard AJ, John TM, Gossger N, Toneatto D, Kittel C, Kimura A, Dull PM. Bacterial antibody persistence two years following meningococcal B vaccination at 6,8,12 months in 40 month old children. European Society for Paediatric Infectious Diseases (ESPID); 2012, 08-12 May, Thessaloniki, Greece Martin NG, Snape MD, Robinson H, John T, Kelly S, Toneatto D, Dull P, Pollard AJ. Reactogenicity and safety of investigational serogroup B meningococcal vaccines given at 40 months of age to primed and vaccine	4CMenB 0.5 mL IM, thigh Recombinant-proteins alone (rMenB)	Phase II RCT Parallel assignment Single-blind (parent/guardian) Single center UK NCT01026974 Endpoints: systemic and local reactions recorded for seven days after immunization. Fever is defined as temperature ≥38°C and graded as severe when ≥ 40 C. Pain is severe if occurring on	"Control" group n=41 Serogroup B meningococcal vaccine naïve age-matched children served as a control group and received two doses of 4CMenB approximately 60 days apart. (at enrolment and at 42 months) Blood samples were taken at enrolment and 30 days after each immunization.	**Local reactogencity**, % of subjects dose 1 , dose2 Pain (severe defined as inability to move limb) 90% (severe 6%), 100% (severe 5%) Erythema (severe defined as > 50mm) 92%, 100% (severe 2%) Induration (severe defined as > 50mm) 41%, 50% Swelling (severe defined as > 50mm) 28%, 41% **Systemic reactogencity, %** of subjects dose 1, dose 2 (severe signs and symptoms not defined) Change in eating habits: 34% (severe 2%), 38% (severe 3%) Sleepiness: 52% (severe 7%), 45% (severe 7%), Vomiting: 2%, 10% Diarrhea: 6%, 5% Irritability: 59%, 68% (severe 4%) Headache: 9,10% Fever: 18%(severe 2%),10% **Serious adverse events** One case of meningoencephalitis considered	Level I NA (poster)

Evidence related to safety of 4CMenB vaccine initiated in children aged 2 to 10 years					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
naïve children European Society for Paediatric Infectious Diseases (ESPID); 2012, 08-12 May, Thessaloniki, Greece		movement of leg, and erythema, induration and swelling severe if greater than 50 mm.		unrelated to the study vaccine. One febrile seizure 8 hours after the second dose of 4CMenB vaccine (fever 39.3°C), no sequelae. Considered possibly related to study vaccine by study authors.	

Evidence related to safety of 4CMenB vaccine initiated in adolescents aged 11 to 17 years

STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Santolaya ME, O'Ryan ML, Valenzuela MT, Prado V, Vergara R, Munoz A, et al. Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study. Lancet 2012 Feb 18;379(9816):617-624.	4CMenB 0.5 mL IM, arm Placebo: 1.5 mg aluminum hydroxide, 10 mM histidine, 110-120 mM saline 0.5 mL IM, arm	Phase IIb/III RCT Parallel assignment Single-blind (observer) Multicenter Chile NCT00661713 Endpoints: Safety of 1, 2 or 3 doses of 4CMenB: frequency of solicited local and systemic reactions 30 min. and within 7 days post injection, and occurrence of other AE and SAEs including medically attended events, throughout study. Safety analyses included all subjects and were descriptive only, with no pre-	N=1,631 enrolled and received 4CMenB vaccine Healthy 11 to 17 year old adolescents Four injections given at 0, 1, 2 and 6 month time points of either 4CMenB vaccine or placebo; at 6 months, subjects in arms 1-3 received either 4CMenB vaccine or placebo (1:2 ratio), arm 4 received placebo, and arm 5 received 4CMenB vaccine: 4CMenB vaccine given at 0 or 0, 6 months with placebo given at 1, 2, 6 or 1, 2 months (n=375, mean age 13.8 years, 1.9 SD, 41% male) 4CMenB vaccine given at 0, 1 or 0, 1,	**Local reactogenicity**, % of subjects, cumulative reactions for all doses of 4CMenB or placebo injections: Pain (severe reaction defined as interference with normal activities) *4CMenB*: 86% any, 17% severe *Placebo*: 60% any, 4% severe p<0.0001 (comparison unclear) Erythema (severe reaction not defined) *4CMenB*: 51% any, 1.5% severe *Placebo*: 28.5% any, 0% severe Induration (severe reaction not defined) *4CMenB*: 40% any, 2% severe *Placebo*: 20.5% any, 1% severe Swelling (severe reaction not defined) *4CMenB*: 39% any, 4% severe *Placebo*: 17% any, 1% severe **Systemic reactogenicity**, % of subjects, cumulative reactions for all doses of 4CMenB or placebo injections (severe reaction defined as interference with normal activities): Malaise *4CMenB*: 51% any, 7% severe *Placebo*: 30% any, 2% severe p<0.0001 for any reaction Myalgia *4CMenB*: 43% any, 6% severe *Placebo*: 23.5% any, 2% severe	Level I, Fair

Evidence related to safety of 4CMenB vaccine initiated in adolescents aged 11 to 17 years

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
		defined statistical criteria; independent data monitoring committee provided guidance for interpretation of safety outcomes; ad hoc analyses for difference between 4CMenB and placebo done using chi square test.	6 months with placebo given at 2, 6 or 2 months (n=375, mean age 13.9 years, 1.9 SD, 43% male) 4CMenB vaccine given at 0, 2 or 0, 2, 6 months with placebo given at 1, 6 or 1 months (n=380, mean age 13.7 years, 1.9 SD, 44% male) 4CMenB vaccine given at 0, 1, 2 months with placebo given at 6 months (n=373, mean age 13.8 years, 1.9 SD, 47% male) 4CMenB vaccine given at 6 months with placebo given at 0, 1, 2 months (n=128, mean age 13.8 years, 2.0 SD, 48% male)	Arthralgia *4CMenB*: 23.5% any, 3.5% severe *Placebo*: 12% any, 1% severe Headache *4CMenB*: 42% any, 5.5% severe *Placebo*: 27% any, 3% severe $p<0.0001$ for any reaction Nausea *4CMenB*: 15% any, 1.5% severe *Placebo*: 11.5% any, 1% severe Stayed home *4CMenB*: 12% *Placebo*: 4% Fever ≥38°C (axillary temperature) *4CMenB*: 4%; *Placebo*: 2% $p<0.0001$ Fever ≥39°C (axillary temperature) *4CMenB*: 1% *Placebo*: <1% $p=0.0689$ Medically attended fever *4CMenB*: <1% *Placebo*: <1% Use of antipyretics *4CMenB*: 4% *Placebo*: 2% $p<0.0002$ **Serious adverse events**: • Juvenile arthritis (n=2): first case occurred 170 days after 3rd dose (0, 1, 2 mo.) of 4CMenB (subject was asymptomatic at study entry, had symptoms of ankle pain and tendinitis before study	

Evidence related to safety of 4CMenB vaccine initiated in adolescents aged 11 to 17 years					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				entry), possibly related to study vaccine; second case occurred 198 days after 3rd dose (0, 1, 2 mo.) of 4CMenB, probably related to study vaccine. • Vasovagal reaction and convulsion (n=1): onset immediately after 1st dose of 4CMenB (subject had a paternal history of epilepsy), judged to be related to the vaccination procedure and not the investigational product. • Death (n=2): due to causes unrelated to vaccination. Study Withdrawal/Discontinuation due to SAE: One subject with juvenile arthritis withdrew and one subject with vasovagal reaction and convulsion led to study discontinuation (both cases are described above).	

Evidence related to safety of 4CMenB vaccine initiated in adults aged 18 to 50 years					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Kimura A, Toneatto D, Kleinschmidt A, Wang H, Dull P. Immunogenicity and safety of a multicomponent meningococcal serogroup B vaccine and a quadrivalent meningococcal CRM197 conjugate vaccine against serogroups A, C, W-135, and Y in adults who are at increased risk for occupational exposure to meningococcal isolates. Clin Vaccine Immunol 2011 Mar;18(3):483-486.	4CMenB 0.5 mL IM, arm	Phase II Single arm study Open label Multicenter Germany, Italy NCT00560313 Endpoints: Solicited reactogenicity and AEs after vaccination [temperature, medication and local and systemic reactions recorded 30 min. and 7 days after each dose; medically attended adverse events, SAEs throughout study; follow-up 6 mo. following last dose of study vaccine].	N=54 enrolled and received 4CMenB vaccine Healthy 18 to 50 year old laboratory workers 4CMenB vaccine given at 0, 2, 6 month time points (n=54, mean age 31.8 years, 6.1 SD, 50% male)	**Local reactogenicity**, % of subjects, all doses combined* (severe reaction defined as inability to perform daily activities) Pain: 98.1% any, 15.5% severe Erythema: 47.1% any, 0.0% severe Induration: 49.0% any, 0.0% severe **Systemic reactogenicity**, % of subjects, all doses combined* Nausea: 13.5% any, 1.3% severe Malaise: 38.1% any, 3.9% severe Myalgia: 37.4% any, 8.4% severe Arthralgia: 27.1% any, 1.9% severe Headache: 31.9% any, 1.3% severe Stayed home: 9.0% Fever (temperature ≥38°C): 1.9% Pyrexia: 2.6% Use of analgesic or antipyretic: 14.2% *Calculated by review authors **Serious adverse events** • Nasopharyngitis (n=6): following 4CMenB vaccine (3 cases after the second dose and 3 cases after the third dose) • Rhinitis (n=3): unclear which vaccine. Study Withdrawal due to SAE: One subject withdrew due to syncope and one subject withdrew due to naspharyngitis, neither considered related to vaccine by investigator.	Level II-1, Fair

Evidence related to safety of 4CMenB vaccine initiated in adults aged 18 to 50 years

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Findlow J, Bai X, Findlow H, Newton E, Kaczmarski E, Borrow R. Safety and immunogenicity of a four component meningococcal group B vaccine (4CMenB) and a quadrivalent meningococcal group A, C, W135 and Y conjugate vaccine (Menveo) in UK laboratory workers with potential occupational exposure to meningococci. International Pathogenic Neisseria Conference (IPNC); 2012, 09-14 September, Würzburg, Germany.	4CMenB Quadrivalent group A, C, W135 and Y conjugate vaccine (MenACW135Y) [Menveo®, Novartis]).	Phase II trial Single arm study UK NCT00962624 Endpoints: Solicited injection site reactions following each vaccination visit; Solicited systemic reactions and use of pain relief following each vaccination visit	N=38 Healthy adults aged 23-55, public health laboratory workers were enrolled and received vaccination in the first visit, N=7 withdrew from the study 4CMenB was given at 0, 3, 6 month time points. Blood samples taken in the same visits and at 2,7 month time points (total 5 visits) Menveo (quadrivalent) was administered concomitantly at 0 months	**Solicited injection site reactions following each vaccination visit** **(extrapolated from figures)** severe reactions not defined Erythema Dose 1:22% Dose2:19% Dose3:42% (severe 3%) Induration Dose 1:41% Dose2:42% (severe 3%) Dose3:51% Pain Dose 1:97% (severe 20%) Dose2: 95% (severe15%) Dose3: 100% (severe 22%) **Solicited systemic reactions and use of pain relief following each vaccination visit** **(extrapolated from figures)** Nause Dose 1(with Menveo®):25% Dose2:18% Dose3:12% Headache Dose 1(with Menveo®):38% Dose2:18% Dose3:17%	Level II-1 N/A (poster)

Evidence related to safety of 4CMenB vaccine initiated in adults aged 18 to 50 years					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
				Fever Dose 1: (with Menveo®)1% Dose2:2% Dose3:1% Use of pain relief Dose 1(with Menveo®):41% Dose2:39% Dose3:30% **Serious adverse events** One episode of nausea and myalgia three days after the second dose.	

Table 6: Summary of evidence related to efficacy of NZ-OMV vaccine

Evidence related to efficacy of NZ-OMV vaccine					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
McNicholas A, Galloway Y, Martin D, Sexton K, O'Hallahan J. Surveillance of vaccine breakthrough cases following MeNZB vaccination. N Z Med J 2008 Apr 18;121 (1272):38-46.	MeNZB™	Prospective cohort, population-based surveillance and additional information obtained from identified vaccine breakthrough cases. Vaccine breakthrough defined as case of epidemic strain IMD with symptom onset > 28 days after 3rd dose of NZ OMV. Questionnaire and blood tests for breakthrough cases to examine host factors.	New Zealand residents aged <20 years	34 cases met definition of vaccine breakthrough, 1 developed IMD 26 days after third dose did not meet case definition. 30/34 completed questionnaire and all appeared to be immune competent based on history. 12/34 had full panel of immune deficiency work-up and all were determined to be immune competent. 8/34 had partial immune work-ups which also indicated immune competence but could not exclude "unlikely event of" terminal complement deficiency or HIV.	Level II-2, Poor (surveillance data is high quality but regarding rule out immune deficiency, hard to make conclusion when only about 1/3 got complete blood tests)
Kelly C, Arnold R, Galloway Y, O'Hallahan J. A prospective study of the effectiveness of the New Zealand meningococcal B vaccine. Am J Epidemiol 2007 Oct 1;166(7):817-823.	MeNZB™	Cohort, population based surveillance and national immunization registry. Multivariate generalized	All New Zealand residents January 2001 to June 2006	Disease rates 3.7 (95% CI: 2.1%, 6.8%) times higher in unvaccinated versus vaccinated individuals Vaccine effectiveness (VE) = 73% (95% CI: 52%, 85%) Estimated that between 2004 and 2006, 54 (95% CI: 22, 115) epidemic strain lab-confirmed cases averted and 1.7 deaths prevented.	Level II-2, Good

Evidence related to efficacy of NZ-OMV vaccine

STUDY DETAILS					SUMMARY
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
		estimating equation rates model to estimate incidence of disease in vaccinated and unvaccinated groups.			
Arnold R, Galloway Y, McNicholas A, O'Hallahan J. Effectiveness of a vaccination programme for an epidemic of meningococcal B in New Zealand. Vaccine 2011 16 September 2011;29(40):7100-7106.	MeNZB™	Cohort, population-based surveillance. VE determined via multivariate Poisson regression comparing risk of serogroup B IMD in vaccinated and unvaccinated individuals, addressed residual confounding by examining VE of MeNZB™ against invasive pneumococcal disease (IPD).	New Zealand residents aged <20 years between 2001 and 2008	*Univariate analysis*: Fully vaccinated vs. unvaccinated, RR = 0.12 (95% CI: 0.05, 0.28) Partially vaccinated vs. unvaccinated, RR = 1.44 (95% CI: 0.90, 2.16) *Multivariate analysis*: *Estimates of VE = 53.3% (95% CI: 25%, 71%) to 76.5% (95% CI: 62%, 85%) * VE varied based on model, most conservative assessed additional protective benefit of MeNZB™ against epidemic serogroup B IMD versus IPD.	Level II-2, Good

Evidence related to efficacy of NZ-OMV vaccine					
STUDY DETAILS					**SUMMARY**
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level and Quality of Evidence**
Galloway Y, Stehr-Green P, McNicholas A, O'Hallahan J. Use of an observational cohort study to estimate the effectiveness of the New Zealand group B meningococcal vaccine in children aged under 5 years. Int J Epidemiol 2009 Apr;38(2):413-418.	MeNZB™	Cohort, population-based surveillance, VE study. Began with vaccine introduction July 2004 and children followed until 24 months after eligible for last dose.	New Zealand residents aged 6 months to <5 years	*VE in fully vaccinated versus unvaccinated persons:* Aged 6 months to <5 years, VE = 80% (95% CI: 52.5%, 91.6%) Aged 6 months to <3 years, VE = 84.8% (95% CI: 59.4%, 94.3%) *VE in partially vaccinated versus unvaccinated persons:* Aged 6 months to <5 years, VE = 71.1% (95% CI: 22.3%, 89.2%) Aged 6 months to <3 years, VE = 71.4% (95% CI: 17.6%, 90.1%) *VE in first 12 months after three doses:* Aged 6 months to <5 years, VE = 81.5% (95% CI: 36.9%, 94.6%) Aged 6 months to < 3 years, VE = 89.2% (95% CI: 46.3%, 97.8%) *VE 13-24 months after three doses:* Aged 6 months to <5 years, VE = 33% (95% CI: -215.7%, 85.8%) Aged 6 months to <3 years, VE = 50.2% (95% CI: -146.5%, 90.0%)	Level II-2, Fair